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A NEW MATHEMATICAL MODEL
FOR NEPHRON MACROMOLECULAR SELECTIVITY

BY

JOHN ANTHONY DOMITER

A THESIS

PRESENTED IN PARTIAL FULFILLMENT OF

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APPROVAL OF THESIS

A NEW MATHEMATICAL MODEL

FOR NEPHRON MACROMOLECULAR SELECTIVITY

BY

JOHN ANTHONY DOMITER

FOR

THE DEPARTMENT OF ELECTRICAL ENGINEERING

NEW JERSEY INSTITUTE OF TECHNOLOGY

BY

FACULTY COMMITTEE

APPROVED: _____

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ABSTRACT

A mathematical model describing the displayed selectivity of the kidney nephron to macromolecules of varying particle size is presented. Diffusion and electrical forces are considered to be the sole mechanisms of transfer. The mass transfer principles responsible for selectivity are considered to occur within the capillary structure, and not within the membrane wall. A charge is assumed to be characteristic of the macromolecule and the membrane wall. Models describing both charged and uncharged solutes are developed.

A non-linear least squares technique, developed by Marquardt, is used to curve fit the derived functions to data relating fractional clearances of dextran and dextran sulfate to varying particle radius. It is shown, that the charged case model gives reasonable results in the simulation of nephron function whrn dextran is the considered solute. Also, curve fittings obtained by the charged case model in the dextran sulfate simulation indicate the realization of charge as a determining variable in the prediction of fractional clearance.

ACKNOWLEDGEMENTS

I would like to express my gratitude to my advisor Dr. Stanley Reisman for the patience, guidance, and technical assistance he has rendered throughout this endeavor. I would also like to thank Dr. John Baumann of the College of Medicine and Dentistry of New Jersey who introduced me to the problem, and Dr. C. R. Huang for his contributions to the development of the model. In addition, I would like to express my graditude to the Electrical Engineering Department of New Jersey Institute or Technology for their interest and support, and to my family and friends, who assisted in the completion of this thesis.

Newark, 1979 John A. Domiter

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CHAPTER 1 : INTRODUCTION

The ability of the kidney to selectively transfer large molecules as a function of particle size has been atributed to the action of the nephron. The application of ultrafiltration theory is popular in the attempt to realize the processes which take place in the nephron. [1,4,5] The filtration theory regards the nephron capillary as a porous structure, having a mean pore radius, and thereby controlling the passage of large molecules by virtue of particle size.

The lack of a physical porous structure in the nephron membrane suggests that approaches other than those offered by filtration principles be investigated to describe the selectivity displayed by the nephron. [17] Also, empirical results, obtained by Bohrer, [3] imply a charge relationship exists in the consideration of transfer of large molecules by the nephron.

The study undertaken here offers an alternate theory, to explain the transfer of large molecules by the nephron. Selectivity is assumed to occur within the capillary, and not ty the action of the membrane. Diffusion and electrical attraction are the forces considered. A model is developed, and is used to simulate results obtained by the Bohrer study.

A non-linear least squares estimation method, developed by Marquardt, is also discussed.[14] The method is implemented to estimate unknown parameters, required by the model in the simulation of the available data. General theory and considerations are presented.

CHAPTER 2 : THE MODEL

2.1 Introduction

Diffusion and electrical forces are considered the mechanisms of mass transfer. The processes are assumed to take place within the nephron capillary, and not in membrane wall. A charge is assumed on both the solute particles and the membrane.

The existence of an electrical charge on the membrane and the solute particles is realized by experimental results obtained by Bohrer,[3] which suggests a charge relationship in the transfer of molecules in the nephron. The model presented here has been developed to simulate the results obtained by the Deen study.

Acknowlegement is given to Dr. C. R. Huang, Professor of Chemical Engineering at New Jersey Institute of Technology, for his generous contributions to the development of the model.

2.2 The General Mass Transfer Equation

The kidney nephron is assumed to be of a tubular structure, having an inside diameter, R , and length, L . The coordinate z is chosen to represent the axial direction, and r the radial (Figure 2.1). The capillary membrane is assumed at $r = R$, and r is zero at the center of the nephron at $z = 0$, and exits at $z = L$.

In the region near the membrane wall, a boundary layer of thickness δ is assumed (Figure 2.2). A primary assumption is that any solute which appears at the membrane wall (at $r = R$) is completely passed across the membrane into the Bowman Space. The Bowman Space is within the glomerulus, and functionally collects all effluent passed by the nephron. [17] For convenience, x is defined, such that:

$$x = r - (R-\delta) \qquad (2.1)$$

and

$$0 \leq x \leq \delta$$

The solutes of interest are comprised of large molecules, such as dextran or dextran sulfate, having positive charge of magnitude q_0 . It is assumed that the molecules are spherical in shape, and have a particle radius, r_p . [1] The capillary membrane is assumed to

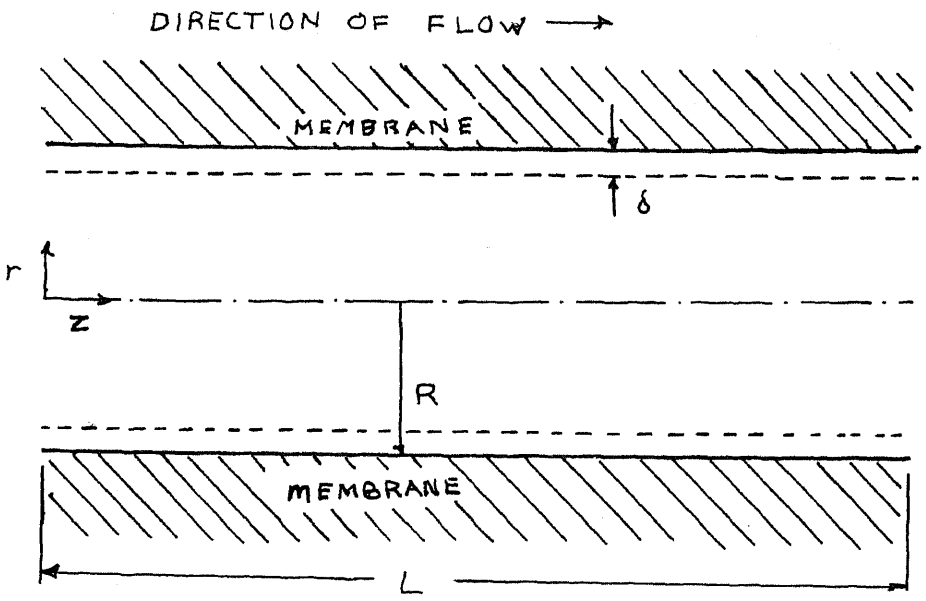

Figure 2.1 - The nephron model

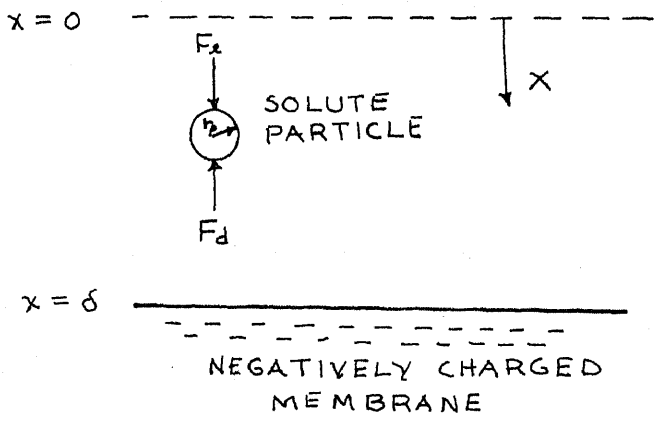

Figure 2.2 - Enlarged view of boundary layer region.

have a negative charge, constant for all values of z at $r = R$, and is responsible for an electric field, $E(x)$ (Section 2.3).

The solute flux is denoted by N_A, and the solute concentration at $x=0$ by C where

$$C = C_o(z)$$

For any constant z, a material balance equation may be written as shown in Equation 2.2,

$$N_A = - \mathcal{D} \frac{dC}{dx} + C v_x \qquad (2.2)$$

where $\mathcal{D}$ is the diffusion coefficient of the solute in water, and v_x is the particle velocity in the x direction. The first term on the right hand side of Equation 2.2 represents the flux contributed to N_A due to Fick's Law (the diffusion of particles due to a concentration gradient) .[6] The second is the flux $c v_x$ caused by the electrical attraction of solute particles by the charged membrane wall. It is noted that

$$v_x = v_x(x)$$

There are two forces acting onaa given particle in the x direction: the Coulomb attraction force,[8,10]

$$F_e = g E(x)$$

and a frictional force due to Stoke's Law, [18]

$$F_d = 6\pi \mu r_p v_x$$

where μ is the viscosity of the fluid medium, in this case, water. In the steady state condition, F_e and F_d will be equal and opposite, and equating the forces and solving for v_x yields

$$v_x = \frac{q E(x)}{6\pi \mu r_p} \tag{2.3}$$

Substituting (2.3) into (2.2) results in

$$N_A = -D \frac{dC}{dx} + \frac{q}{6\pi \mu r_p} E(x) C \tag{2.4}$$

It can be assumed, that for any constant z, the solute flux remains constant with respect to x:

$$\frac{d N_A}{d x} = 0 \tag{2.5}$$

Differentiating (2.4), and taking advantage of (2.5), yields

$$\frac{d^2 C}{dx^2} - K_1 E(x) \frac{dC}{dx} - K_1 \frac{dE(x)}{dx} C = 0 \tag{2.6}$$

where

$$K_1 = \frac{q}{6\pi \mu r_p D}$$

The electric field can be expressed in the following exponential form (see Section 2.3):

$$E(x) = E_0 e^{-ax} \tag{2.7}$$

Equation 2.6 may then be written

$$\frac{d^2C}{dx^2} - K_1 E_0 e^{-ax} \frac{dC}{dx} + K_1 E_0 a e^{-ax} C = 0 \tag{2.8}$$

and when integrated, yields

$$\frac{dC}{dx} - K_1 E_0 e^{-ax} C = c_1 \tag{2.9}$$

where c_1 is a constant of integration, and refering to Equation 2.2

$$c_1 = -\frac{N_A}{\mathcal{D}} \tag{2.10}$$

Using an appropriate integrating factor, Equation 2.9 may be integrated, and

$$C = \frac{c_1 \int \exp\left(\frac{K_1 E_0}{a} e^{-ax}\right) dx + c_2}{\exp\left(\frac{K_1 E_0}{a} e^{-ax}\right)} \tag{2.11}$$

In order to find an expression for N_A in terms of z, two boundary conditions are needed. When $x = 0$, the concentration C is equal to C_0, constituting the first boundary condition. At the membrane wall (when $x = \delta$), the flux is assumed directly proportional to the concentration by a constant, β. Substituting the first condition into Equation 2.10 results in a solution for c_2.

$$c_2 = C_0(z) \exp\left(\frac{K_1 E_0}{a}\right) \tag{2.12}$$

Combining Equations 2.10, 2.11, and 2.12, and the second boundary condition:

$$c_1 = -C_0(z) \frac{\beta \exp\left(\frac{K_1 E_0}{a}\right)}{\delta \exp\left(\frac{K_1 E_0}{a} e^{-a\delta}\right) + \beta \int_0^{\delta} \exp\left(\frac{K_1 E_0}{a} e^{-a\chi}\right) d\chi} \tag{2.13}$$

or more consisely

$$c_1 = -C_0(z)\, M$$

and

$$N_A = N_A(z)$$

$$= C_0(z)\, M\, \delta \tag{2.14}$$

In the development of a material balance expression with respect to the axial direction, a differential cylindrical element is considered (Figure 2.3). The element is positioned at some z , and has a length Δz , and radius R . Three surfaces are formed, and the amount of solute which enters the element through the normal plane at $z = z$ must equal that amount which exits at $z = z + \Delta z$, and through the cylinder wall:

$$\bar{v}_z \pi R^2 C_0(z)\Big|_{z=z} - \bar{v}_z \pi R^2 C_0(z)\Big|_{z=z+\Delta z} - N_A 2\pi R \Delta z = 0 \tag{2.15}$$

where $\bar{v}_z$ is the mean velocity of the solute with respect to the z direction. Allowing $\Delta z \to 0$, the differential

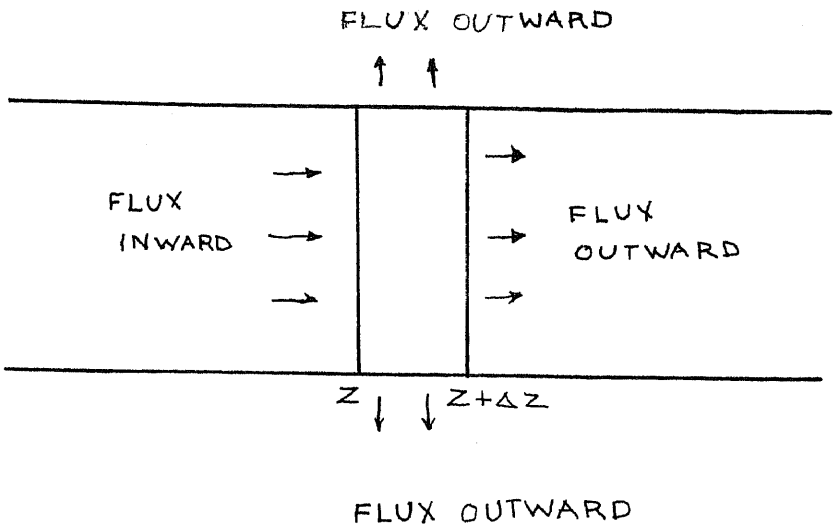

Figure 2.3 - Differential cylindrical element

equation

$$\bar{v}_z \pi R^2 \frac{dC_o(z)}{dz} + N_A 2\pi R = 0 \qquad (2.16)$$

may be formed, and by Equation 2.14

$$\frac{dC_o(z)}{dz} + \frac{2\mathcal{D}M}{\bar{v}_z R} C_o(z) = 0 \qquad (2.17)$$

Equation 2.17 is easily solvable by separation of varible techniques, and

$$C_o(z) = c_3 \exp\left(\frac{-2\mathcal{D}M}{\bar{v}_z R} z\right) \qquad (2.18)$$

and c_3 is found by noting that at $z=0$, $C_o(z) = C_o(0)$, and

$$C_o(z) = C_o(0) \exp\left(\frac{-2\mathcal{D}M}{\bar{v}_z R} z\right) \qquad (2.19)$$

The total amount of solute transferred across the membrane is obtained by integrating the flux N_A along the axial direction

$$\omega = \int_0^L 2\pi R N_A \, dz \qquad (2.20)$$

By Equation 2.14

$$\omega = \int_0^L 2\pi R \mathcal{D} C_0(z) M \, dz \qquad (2.21)$$

and substituting $C_0(z)$ from Equation 2.19

$$\omega = K_2 \int_0^L \exp\left(\frac{-2\mathcal{D}M}{\bar{v}_2 R} z\right) dz \qquad (2.22)$$

where ω is the amount of solute passed through the membrane, and

$$K_2 = 2\pi R \mathcal{D} M C_0(0)$$

Integration yields:

$$\omega = \pi R^2 \bar{v}_2 \, C_0(z=0)\left(1 - \exp\left(\frac{-2\mathcal{D}M}{\bar{v}_2 R} L\right)\right) \qquad (2.23)$$

Assuming that all of the parameters on the right hand side of Equation 2.23 are held constant, with the exception of r_p and $\mathcal{D}$, the amount of solute transferred becomes a function of r_p and $\mathcal{D}$ only.

2.3 The Electric Field

The capillary membrane is assumed to be uniformly charged, and in contact with the solvent-solute mixture. Solute particles of opposite charge, drawn near to the membrane surface, will decrease the charge "seen" by the particles further from the membrane, thereby decreasing their attraction.

A potential of $-\psi_0$ is assumed at the membrane surface, and due to the interaction of the surface and particles, a potential function, $\psi(x)$, may be defined. In this instance, the magnitude of the potential decreases as one proceeds from the membrane into the solution. The variation of solute concentration, C, due to the electrical considerations is [7]

$$C = C_0 e^{-q\psi(x)/\kappa T} \qquad (2.24)$$

where, q is the particle charge, κ is the Boltzmann constant, T the temperature (°K), and C_0 is the concentration of solute far from the membrane surface.

At any constant z, the charge density ρ is given by

$$\rho = qC \qquad (2.25)$$

Since the charge density ρ for any value of x or z, is defined, Poisson's equation may be used to find the

divergence of the gradient of the electrical potential at that point:

$$\nabla^2 \psi = - \frac{4\pi\rho}{D} \qquad (2.26)$$

where ∇^2 is the Laplacian operator, and D is the dielectric constant of the solvent.[7]

Various solutions of Equation 2.26 have been studied;[7,8] one such solution is for a polyionic system, and assuming $q\psi$ is small compared with κT, Equation 2.26 becomes

$$\nabla^2 \psi = a \psi \qquad (2.27)$$

where

$$a = \left(\frac{4\pi}{D\kappa T} \sum_i C_{o,i} q_i^2 \right)^{1/2}$$

and C_o and q are the initial concentration and charge of the ith particle. The solution for the unidimentional (x) and single particle case is approximated by

$$\psi = \psi_o e^{-ax} \qquad (2.28)$$

for small values of ψ_o and q. Further simplification is achieved by assuming the initial concentration is constant over all z , which is useful in evaluating the total solute transferred (Section 2.2).

The expression for $E(x)$ is given by:[10]

$$E(x) = - \frac{d\psi}{dx} \qquad (2.29)$$

or

$$E(x) = E_o \, e^{-ax} \tag{2.30}$$

where

$$E_o = -\psi_o \, a$$

2.4 The Diffusion Coeffcient

In Section 2.2, Equation 2.23 gives an expression for the total solute lost as a function of the particle radius, r_p, and the diffusion coefficient, $\mathcal{D}$. The coefficient, however, is not independendent of the particle radius, but can be expressed as a function of r_p.

Data regarding the permeability of dextran is not readily accessable, however, it is assumed that the diffusion can be expressed by

$$\mathcal{D} = K_{\mathcal{D}} / r_p^{n} \qquad (2.31)$$

where $K_{\mathcal{D}}$ is defined as the diffusion constant, and $n > 0$. A typical value of n in mass transfer applications such as this is 2.[11]

2.5 The Complete Model

Fractional clearance, an indication of kidney function, is defined as [1]

$$\theta = \frac{(U/P)_{dextran}}{(U/P)_{inulin}} \qquad (2.32)$$

where U is the solute concentration in urine, P, the concentration in plasma. The subscript denotes the solute of interest.

Inulin is a substance which freely passes through the nephron membrane and does not reabsorb into the efferent plasma [18] and therefore, the inulin concentration of the urine is eqivalent to the Bowman inulin concentration. Also, since all of the inulin is passed through the membrane, the denominator of Equation 2.23 becomes unity, and

$$\theta = (U/P)_{dextran} \qquad (2.33)$$

when the solute is dextran. If it is assumed that the solute is not reabsorbed, as in the case of dextran, then θ can be expressed [1]

$$\theta = \frac{C_{SB}}{C_{SA}} \qquad (2.34)$$

where C_{SB} is the solute concentration in the Bowman Space, and C_{SA} is the concentration at the afferent end of the nephron. For small σ (Section 2.2), C_{SA} may be con-

sidered to equal to $C(z=0)$, and therefore

$$\theta = \frac{C_{SB}}{C(z=0)} \tag{2.35}$$

It is assumed that the solvent volume flux is constant crossing the membrane, and hence, the concentration will be directly proportional to the amount of solute crossing the membrane:

$$C_{SB} = K_P \omega \tag{2.36}$$

where K_P is a proportionality constant, and ω is the solute transferred. Equation 2.35 may be written

$$\theta = \frac{K_P \omega}{C(z=0)} \tag{2.37}$$

and in complete form (from Equation 2.23)

$$\theta = \theta(r_p) = \pi K_P R^2 \bar{v}_2 \left(1 - \exp\left(\frac{-2\vartheta M L}{\bar{v}_2 R}\right)\right) \tag{2.38}$$

where

$$\vartheta = \frac{K_D}{r_p^n}$$

$$M = \frac{\beta \exp\left(\frac{K_1 E_0}{a}\right)}{\vartheta \exp\left(\frac{K_1 E_0}{a} e^{-a\delta}\right) + \beta \int_0^{\delta} \exp\left(\frac{K_1 E_0}{a} e^{-ax}\right) dx}$$

$$K_1 = \frac{e}{6\pi\mu r_p \vartheta}$$

$$E_0 = -\psi_0 a$$

$$a = \left(\frac{4\pi}{DKT} C_0(z=0) e^2\right)^{1/2}$$

and the parameters listed are previously defined (Sections 2.2, 2.3, and 2.4).

For the special case of an uncharged solute, $g = 0$, and therefore

$$M = \frac{\beta}{\vartheta + \beta\delta} \qquad (2.39)$$

and

$$K_1 = E_0 = \alpha = 0$$

CHAPTER 3 : MARQUART'S METHOD OF LEAST SQUARES

3.1 Introduction

Numerical computation of Equation 2.38 requires the estimation of parameter values which are not availible. Due to the non-linearity of the model function, simple linear least squares curve fitting schemes could not be implemented, and attention was drawn towards other techniques, An iterative method, developed by Marquardt, [14] was chosen to perform the iteration.

Marquardt's method of least squares estimation of non-linear parameters is a compromise between the Taylor Series and the Gradient methods of obtaining non-linear least squares solutions. Seperately, both methods have their difficulties in obtaining an accurate solution. The method selected, however, incorporates both methods such that the shortcomings of either method are minimized.

3.2 Non-Linear Least Squares

A model function is assumed to be of the form

$$E(y) = f(x_1, x_2, \cdots, x_m; B_1, B_2, \cdots, B_K) \qquad (3.1)$$

$$= f(\underline{x}, \underline{B})$$

where x_m are independent varibles, B_K are the K parameters, and $\underline{\ }$ denotes matrix notation. The i data points are denoted by

$$(Y_i, X_{1i}, X_{2i}, \cdots, X_{mi}) \qquad i = 1, 2, \cdots, n .$$

The problem is to compute those estimates of the parameters which will minimize some residual, ϕ , such that

$$\phi = \sum_{i=1}^{n} (Y_i - \hat{Y}_i)^2 \qquad (3.2)$$

where $\hat{Y}_i$ is the predicted value of y at the i th data point.

The Taylor Series method begins its approach by initally expanding the function

$$\hat{Y}(\underline{X}_i, \underline{b} + \underline{\delta}_t) = f(\underline{X}_i, \underline{b}) + \sum_{j=1}^{K} \left(\frac{\partial f_i}{\partial b_i}\right)(\delta_t); \qquad (3.3)$$

or concisely

$$\underline{\hat{Y}} = \underline{f_o} + P\,\underline{\delta_t} \qquad (3.4)$$

$\underline{b}$ represents the parameter vector, and $\underline{\delta_t}$ is an incremental

correction to $\underline{b}$. The value of ϕ predicted, $\langle\phi\rangle$, is

$$\langle\phi\rangle = \sum_{i=1}^{n} \left(Y_i - \hat{Y}_i \right)^2 \qquad (3.5)$$

Since δ_t is linear in Equation (3.4), a solution for δ_t may be found corresponding to a minimum $\langle\phi\rangle$. Setting $\frac{\partial \langle\phi\rangle}{\partial \delta_j} = 0$ for all j , the equation becomes

$$\underline{A}\ \underline{\delta_t} = \underline{g} \qquad (3.4)$$

where

$$A^{[K\times K]} = P^T P \qquad (3.5)$$

$$P^{[n\times K]} = \left(\frac{\partial f_i}{\partial b_j}\right) \qquad \begin{matrix} i = 1,2,\cdots,n \\ j = 1,2,\cdots,K \end{matrix} \qquad (3.6)$$

$$g^{[K\times 1]} = \left(\sum_{i=1}^{n} (Y_i - f_i)\frac{\partial f_i}{\partial b_j}\right) \qquad j = 1,2,\cdots,K \qquad (3.7)$$

$$= P^T \left(\underline{Y} - \underline{f_o}\right) \qquad (3.8)$$

Once a solution is found for $\underline{\delta_t}$, it is added to the original estimate, and the forementioned procedure is repeated until $\underline{\delta_t}$ becomes of little contribution to $\underline{b}$.

The success of obtaining a reasonable estimate by means of the Taylor Series method is dependent upon careful choice of the initial estimates. In the non-linear case, contours of constant ϕ are severely distorted in regions far from the minimum. Near the minimum, however,

the contours become eliptical, as in the linear case, and proper convergence of the Taylor series takes place.[12,15] Trials made far from the region of convergence may cause divergence of the series, and erroneous estimations of the parameters.

An alternative to the Taylor Series procedure is the Gradient method. Here, the correction vector is given by the negative gradient of ϕ :

$$\underline{\delta_j} = -\left(\frac{\partial \phi}{\partial b_1}, \frac{\partial \phi}{\partial b_2}, \cdots, \frac{\partial \phi}{\partial b_k}\right)^T \qquad (3.9)$$

In practice, initial values may be chosen far from the effective region of the Taylor Series method. Unfortunately, convergence of the Gradient solution in the region of the minimum is relatively slow, a consideration which renders neither method ideal.

Marquardt's least squares method incorporates both previously mentioned methods, such that, it relies upon the Gradient method at the beginning of the iterative process, and as the minimum of ϕ is approached, the Taylor Series method continues the calculations. Using this method, poor estimation of initial parameters need not inhibit convergence of a solution in a minimum of iterations.

3.3 Marquardt's Method of Least Squares Estimation

It has been shown,[14] that a solution for the Gradient correction vector, $\underline{\delta_g}$, may be obtained by the solution of

$$(\underline{A}^* + \lambda \underline{I})\, \underline{\delta_g}^* = \underline{g}^* \tag{3.10}$$

where $\underline{A}^*$, $\underline{\delta_g}^*$, and $\underline{g}^*$ are scaled versions of the vectors defined Section 3.2 . $\underline{\delta_t}$ may may be found from

$$\underline{A}^*\, \underline{\delta_t}^* = \underline{g}^* \tag{3.11}$$

and δ_j in both cases is found by the transformation

$$\delta_j = \delta_j^* / \sqrt{a_{jj}} \tag{3.12}$$

Marquardt's algorithm considers the value of ϕ at the r th iteration, or $\phi^{(r)}$. Equation (3.10) then becomes

$$(\underline{A}^{*(r)} + \lambda^{(r)} \underline{I})\, \underline{\delta}^{*(r)} = \underline{g}^{*(r)} \tag{3.13}$$

and when solved, yields $\underline{\delta}$, a new trial vector

$$\underline{b}^{(r+1)} = \underline{b}^{(r)} + \underline{\delta}^{(r)}$$

and a new residual $\phi^{(r+1)}$. The values of $\phi^{(r)}$ and $\phi^{(r+1)}$ are dependent upon the value of at the rth iteration, $\lambda^{(r)}$. Inspection of Equations (3.10) and (3.11) illustrates, that as λ decreases, the Gradient solution begins to approach the Taylor Series solution.

The iterative process seeks to minimize the residual,

such that

$$\phi^{(r+1)} < \phi^{(r)}$$

Since ϕ is a function of λ, the algorithm chooses some λ, such that the minimum of ϕ is obtained. The strategy is as follows:[14]

Let $\nu > 1$

Compute $\phi(\lambda^{(r-1)})$ and $\phi(\lambda^{(r-1)}/\nu)$

1. If $\phi(\lambda^{(r-1)}/\nu) \leq \phi^{(r)}$, let $\lambda^{(r)} = \lambda^{(r-1)}/\nu$

2. If $\phi(\lambda^{(r-1)}/\nu) > \phi^{(r)}$, and $\phi(\lambda^{(r-1)}) < \phi^{(r)}$, let $\lambda^{(r)} = \lambda^{(r-1)}$

3. If $\phi(\lambda^{(r-1)}/\nu) > \phi^{(r)}$, and $\phi(\lambda^{(r-1)}) > \phi^{(r)}$, increase λ by successive multiplication by ν until for some smallest ω, $\phi(\lambda^{(r-1)} \nu^{\omega}) \leq \phi^{(r)}$
   Let $\lambda^{(r)} = \lambda^{(r-1)} \nu^{\omega}$

In practice, an initial λ and a value for ν is needed (Marquardt suggests 10^{-2} and 10 respectively). The iteration is converged when the correction to the parameters becomes small,:

$$\frac{|\delta_j^{(r)}|}{\tau + |b_j^{(r)}|} < \varepsilon \qquad \text{for all } j$$

where τ and ε are arbitrary values.

It is expected that a well behaved function allows for smaller and smaller λ, so that in the linearized

region of minimum ϕ, the Taylor Series is allowed to perform the convergence. Added conditions to the method are included to satisfy minimum ϕ, and therefore, a feasible neighborhood is always obtained. It must be noted, that care must be yet be taken in the choice of initial estimates of the parameters and in computation of the algorithm to allow for accurate results.

CHAPTER 4 : SIMULATION OF THE MODEL

4.1 Introduction

Implementation of Marquardt's least squares method required that the model functions be expressed as a function of the independent variable and the unknown parameters to be estimated. Also, since poor estimates for initial values causes convergence difficulties, a technique was used such that reasonable estimates were obtained.

4.2 Simulation Method

Parameters, for which estimates were desired, were defined in terms of the model parameters. These were chosen in such a manner, that information regarding the model parameters could be extracted. Analytic partial derivatives of the transformed function with respect to the partial derivatives were calulated.

Prior to use of the least squares method, intial estimates were investigated. Since many of the values of the parameters were not available, trial and error insertion of values into the functions was used. In all cases, values were implemented in the models, and varied, noting the behavior of the function to these variations. Once a set of values displayed a reasonable representation of experimental results, Marquart's method was initated. In this manner, a higher incidence of convergence was expected.

After convergence of the parameters was accomplished by least squares, the iterated values were used to generate data, which was compared to experimental results. Execution of the entire forementioned procedure was repeated many times to obtain an accurate and singular fit.

All calculations were computer aided. A Fortran version of Marquardt's algorithm is described in Appendix

I . All integrations involved in the entire process were performed numerically by Simpson's Rule.

4.3 Parameter Selection - Charged Case

The model function for the fractional clearance of a charged solute is given by Equation 2.38 . The parameters to be estimated were chosen as follows:

Let

$$B_1 = \pi K_p R^2 \bar{v}_z \tag{4.1}$$

$$B_2 = 2L / \bar{v}_z R \tag{4.2}$$

$$B_3 = 1 / 6\pi\mu \tag{4.3}$$

$$B_4 = a \tag{4.4}$$

$$B_5 = \psi_0 a \tag{4.5}$$

$$B_6 = \beta \tag{4.6}$$

$$B_7 = K_D \tag{4.7}$$

and

$$B_8 = -1 + \eta \tag{4.8}$$

Substitution of these values into the model equation transforms θ into a function of r_p and B_k:

$$\theta = B_1 \left[1 - \exp\left[\frac{-B_2 B_6 \exp\left(\frac{-B_3 B_5}{B_7 r_p^{-B_8}}\right)}{\exp\left(\frac{-B_3 B_5}{B_7 r_p^{-B_8}} e^{-a\delta}\right) + \frac{B_6}{B_7 r_p^{(B_8-1)}} \int_0^{\delta} \exp\left(\frac{-B_3 B_5}{B_7 r_p^{-B_8}} e^{-a\chi}\right) d\chi} \right] \right] \quad (4.9)$$

where all values are positive.

4.4 Parameter Selection - Uncharged Case

The model function for the fractional clearance of an uncharged solute is given by Equations 2.38 and 2.39 . The adjustable parameters were chosen as follows:

Let

$$B_1 = \pi K_p R^2 \bar{v}_2 \tag{4.10}$$

$$B_2 = -2L\beta / \bar{v}_2 R \tag{4.11}$$

$$B_3 = \beta / K_\theta \tag{4.12}$$

and

$$B_4 = n \tag{4.13}$$

Under these assumptions, θ becomes

$$B_1 \left(1 - \exp \frac{B_2}{1 + B_3 r_p^{B_4}} \right) \tag{4.14}$$

where all parameters are positive valued.

CHAPTER 5 : RESULTS

5.1 Considerations

The data available was taken from a study, in which the fractional clearances were measured with respect to particle radius of infused dextran and dextran sulfate. For each of the solutes, a comparative study was performed, such that the effect of angiotensin II was investigated. Angiotensin is a substance which induces proteinuria, a condition by which large plasma protein molecules, which normally do not transfer into the urine, pass through the nephron membrane freely. [3.17] Fractional clearances were measured for both solutes under normal hydropenia conditions, and also when angiotensin was infused. Tables 5.1, 5.2, 5.3, and 5.4 summarize the empirical results found in the Deen study.

An extensive literature search was undertaken, in order to determine empirical values for the parameters used in the simulation. Unfortunately, the lack of existing data rendered little insight into the nature of the values required. Trial and error estimates for all of the parameters were made according to the technique outlined in Section 4.2 .

For each of the curve fits accomplished, the experimental and predicted fractional clearances were tabulated

and plotted. The iterated parameter values were recorded to obtain comparison between the different trial cases.

Table 5.1

Fractional clearance of dextran of varying molecular size measured under normal hydropenia. [3]

Particle Radius r_p (Å)	Fractional Clearance θ_{meas}
18	1.00
20	0.97
22	0.87
24	0.73
26	0.60
28	0.45
30	0.32
32	0.22
34	0.15
36	0.09
38	0.045
40	0.022
42	0.008

Table 5.2

Fractional clearance of dextran of varying molecular size measured under angiotensin infusion.[3]

Particle Radius r_p (Å)	Fractional Clearance θ_{meas}
18	1.00
20	0.99
22	0.95
24	0.85
26	0.74
28	0.59
30	0.46
32	0.32
34	0.22
36	0.14
38	0.075
40	0.038
42	0.019

Table 5.3

Fractional clearance of dextran sulfate of varying molecular size measured under normal hydropenia.[3]

Particle Radius r_p (Å)	Fractional Clearance θ_{meas}
18	0.56
20	0.35
22	0.19
24	0.11
26	0.06
28	0.032
30	0.020
32	0.013
34	0.007
36	0.003
38	0.0009
40	0.0004
42	0.0002

Table 5.4

Fractional clearance of dextran sulfate of varying molecular size under angiotesin infusion. [3]

Particle Radius r_p (Å)	Fractional Clerance θ_{meas}
18	0.74
20	0.55
22	0.37
24	0.25
26	0.16
28	0.099
30	0.062
32	0.039
34	0.021
36	0.010
38	0.0032
40	0.0009
42	0.0005

5.2 The Uncharged Case

The model derived for the uncharged case was used exclusively in simulations, where dextran was the infused solute. Because of its molecular structure, it was assumed that the net charge on a single dextran molecule was zero. The zero case model was not applied to studies using dextran sulfate as the solute.

In the implementation of the least squares curve fit, weighting of the residual function was investigated. For each of the fits attempted, the following weighting functions were implemented:

$$\phi = 1.0 \sum \left(Y_i - \hat{Y}_i \right)^2 \qquad (5.1)$$

$$\phi = \sum \frac{1}{Y_i} \left(Y_i - \hat{Y}_i \right)^2 \qquad (5.2)$$

$$\phi = \sum \frac{1}{(Y_i)^2} \left(Y_i - \hat{Y}_i \right)^2 \qquad (5.3)$$

The functions are such that, importance is given to those values of fractional clearance which are small in comparison to values corresponding to smaller radii. It was found that Equation 5.2 yielded the most profitable curve fits, and the results presented in this section are representative of this weighting.

Initially, η was considered as a constant fixed

parameter, such that $\eta = 2$. The results are summarized in Table 5.5 and Figures 5.1 and 5.2.

The incorporation of η as an adjustable parameter led to the inability of obtaining a convergent solution of the least squares algorithm. However, a solution was obtained by considering only particle radii larger than 26 Å . The results are summarized in Table 5.6 and Figures 5.3 and 5.4 .

Table 5.5

Fractional clearance values of dextran of varying molecular size predicted by the zero charge model, and holding during the curve fit.

Particle Radius r_p (Å)	Fractional Clearances Predicted Under Normal Hydropenia θ_{CALC}	Fractional Clearances Predicted Under Angiotensin Infusion θ_{CALC}
18	0.75	0.79
20	0.67	0.72
22	0.61	0.65
24	0.56	0.60
26	0.52	0.55
28	0.48	0.51
30	0.45	0.48
32	0.42	0.45
34	0.40	0.42
36	0.38	0.40
38	0.36	0.38
40	0.34	0.36
42	0.32	0.34
Iterated Parameter Estimates		
B_1	542.2	810.4
B_2	1.32	2.18
B_3	5.31×10^{10}	1.22×10^{10}

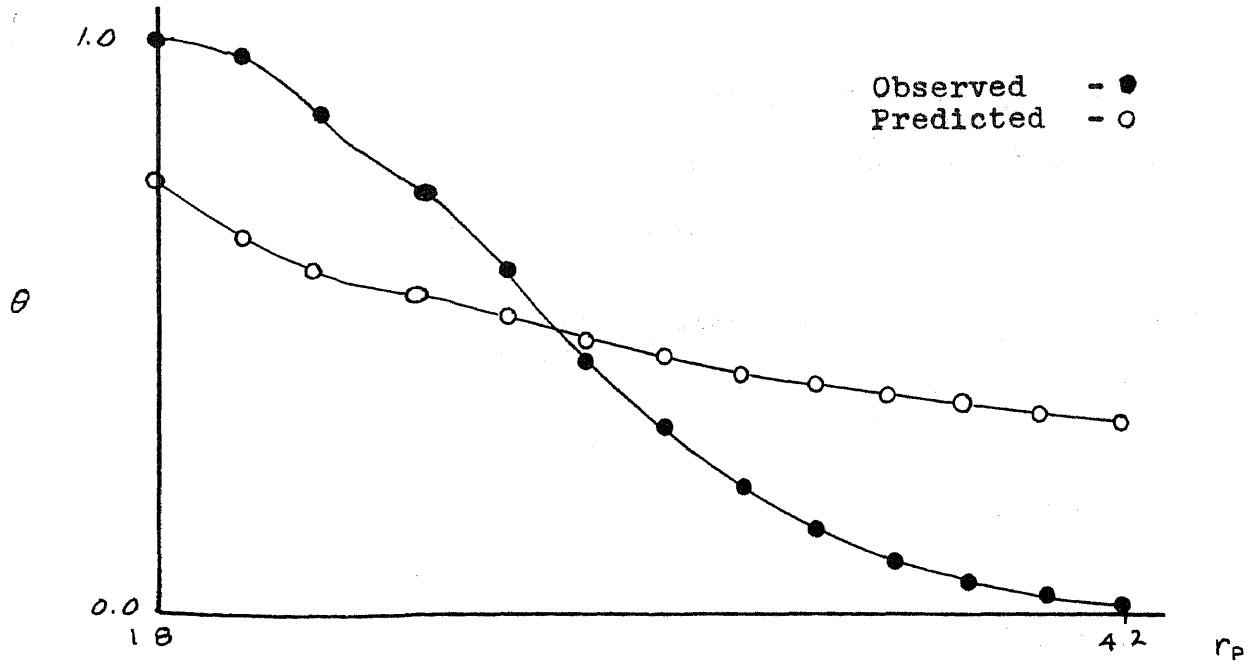

Figure 5.1 - Fractional clearance versus particle radius for dextran under normal hydropenia using the zero charge case model and $n=2$.

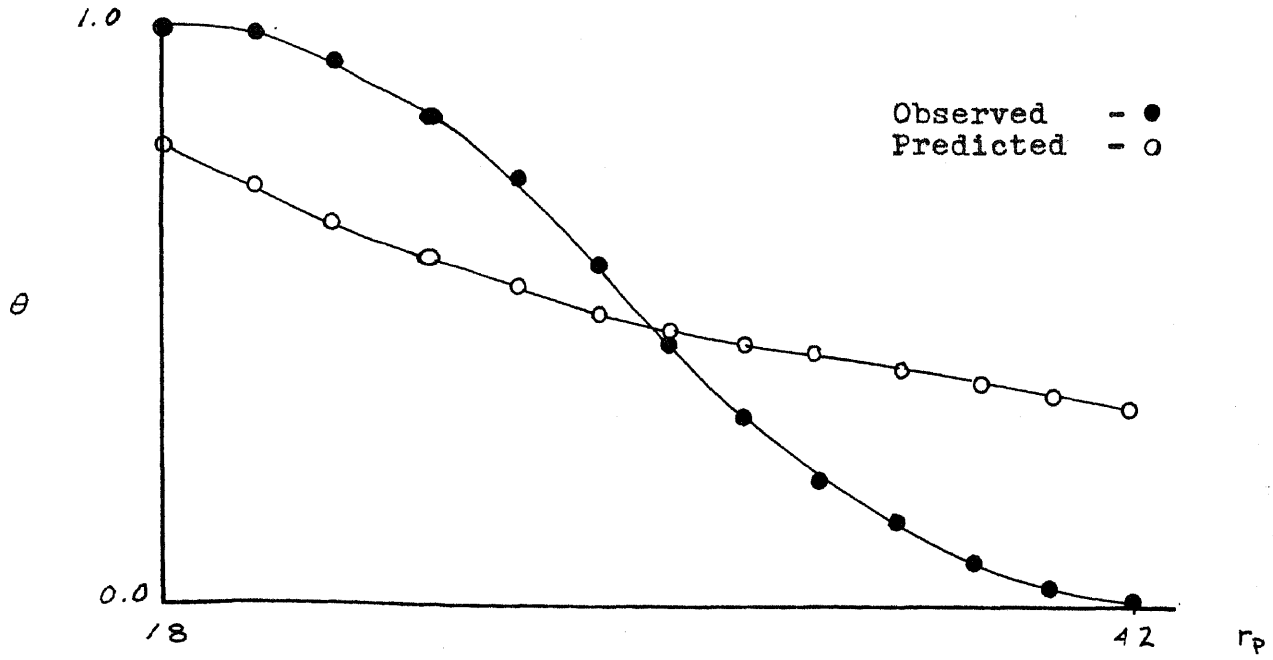

Figure 5.2 - Fractional clearance versus particle radius for dextran under angiotensin induced conditions using the zero charge case model and $n=2$.

Table 5.6

Fractional clearance values of dextran of varying molecular size predicted by the zero charge model, for particle radii greater than 26 A , for variable η .

Particle Radius	Fractional Clearances Predicted Under Normal Hydropenia	Fractional Clearances Predicted Under Angiotensin Infusion
r_p (Å)	θ_{CALC}	θ_{calc}
28	0.045	0.092
30	0.037	0.081
32	0.031	0.071
34	0.026	0.064
36	0.022	0.057
38	0.019	0.051
40	0.016	0.046
42	0.014	0.041
Iterated Parameter Estimates		
B_1	1.02	0.95
B_2	1.03	1.00
B_3	9.43×10^6	9.05×10^6
B_4	3.04	2.21

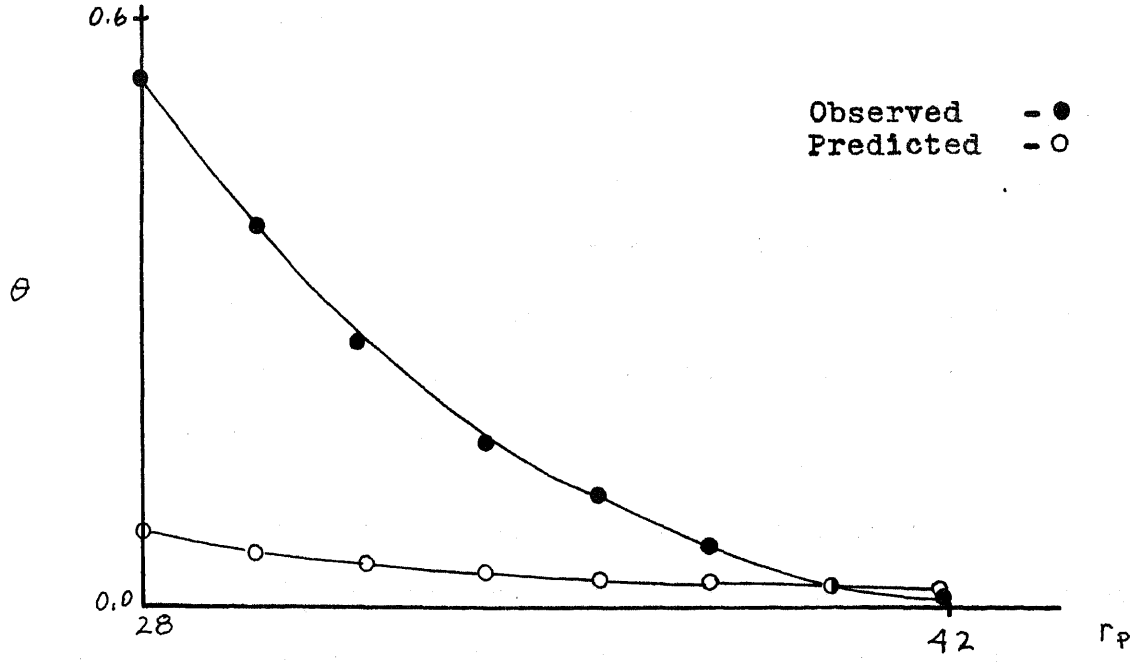

Figure 5.3 - Fractional clearance versus particle radius for dextran under normal hydropenia using the zero charge case model .

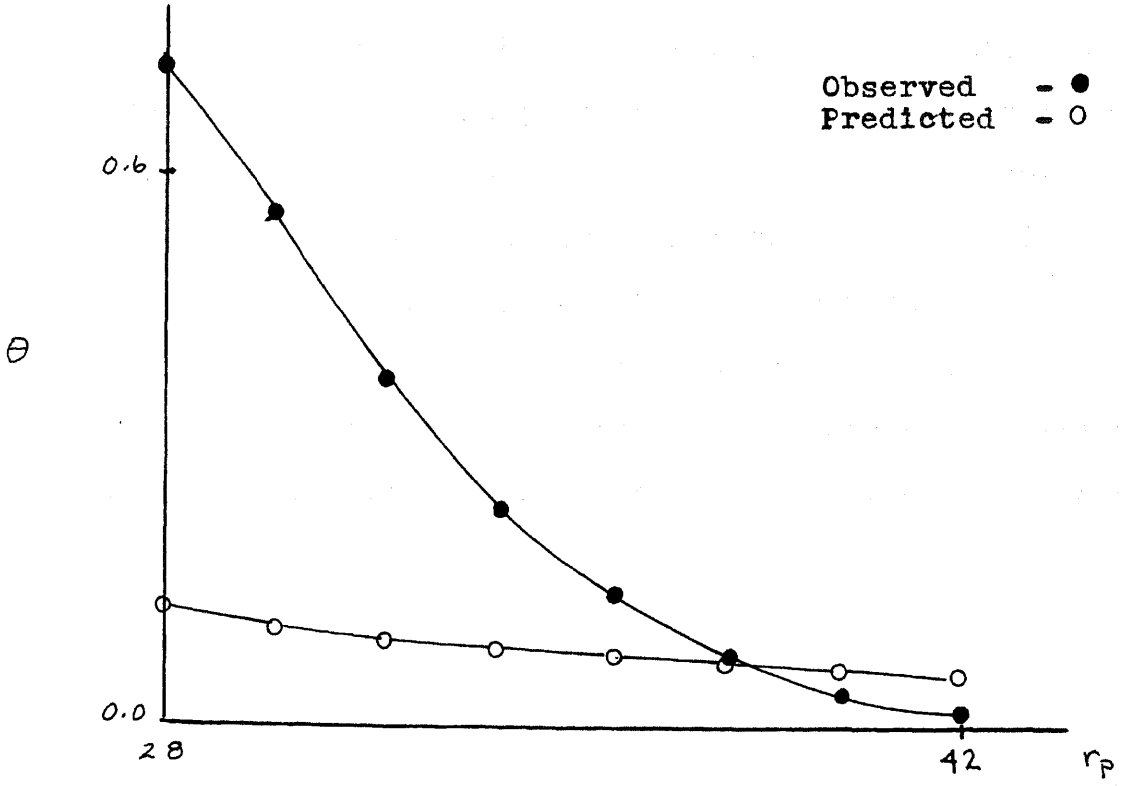

Figure 5.4 - Fractional clearance versus particle radius for dextran under angiotensin induced conditions using the zero charge case model .

5.3 The Charged Case

The model derived in Section 4.3 was used to curve fit all of the experimental cases, and for all, convergence of parameter estimates was obtained. The technique of simulation used is again outlined in Section 4.2 . A residual weighting function was not incorporated in the least squares fits.

The parameter δ was not considered in the choice of adjustable parameters. For convenience, δ was estimated by implementing different values of δ , and regarding that value which resulted in an optimal fit. For all cases, the value of $\delta = 10^{-3}$.

Tables 5.7 and 5.8 give the observed and predicted data of the experiment performed using dextran in normal hydropenia and angiotensin induced conditions respectively. Graphical results are given in Figures 5.5 and 5.6. Tables 5.9 and 5.10 display the results found by considering the data found by using dextran sulfate as the solute, and normal hydropenia and angiotensin induced conditions. Graphical results are also displayed in Figures 5.7 and 5.8 .

Table 5.7

Observed and predicted values of fractional clearance versus particle radius for dextran under normal hydropenia using the charged case model.

Particle Radius r_p (Å)	Observed Fractional Clearance θ_{meas}	Predicted Fractional Clearance θ_{CALC}
18	1.00	1.02
20	0.97	0.95
22	0.87	0.86
24	0.73	0.74
26	0.60	0.60
28	0.45	0.46
30	0.32	0.33
32	0.22	0.22
34	0.15	0.13
36	0.09	0.08
38	0.045	0.039
40	0.022	0.019
42	0.008	0.008

Iterated Parameter Estimates

B_1	1.23
B_2	5.71
B_3	1.04
B_4	1.07×10^3
B_5	1.04
B_6	0.50
B_7	9.59×10^{-21}
B_8	3.00

Table 5.8

Observed and predicted values of fractional clearance versus particle radius for dextran under angiotensin induced conditions using the charged case model.

Particle Radius	Observed Fractional Clearance	Predicted Fractional Clearance
r_p (Å)	θ_{meas}	θ_{calc}
18	1.00	1.01
20	0.99	0.98
22	0.95	0.93
24	0.85	0.85
26	0.74	0.74
28	0.59	0.60
30	0.46	0.46
32	0.32	0.33
34	0.22	0.21
36	0.14	0.13
38	0.075	0.070
40	0.038	0.035
42	0.019	0.016

Iterated Parameter Estimates

B_1	1.08
B_2	7.00
B_3	1.03
B_4	1.06×10^3
B_5	1.03
B_6	0.63
B_7	9.65×10^{-21}
B_8	3.00

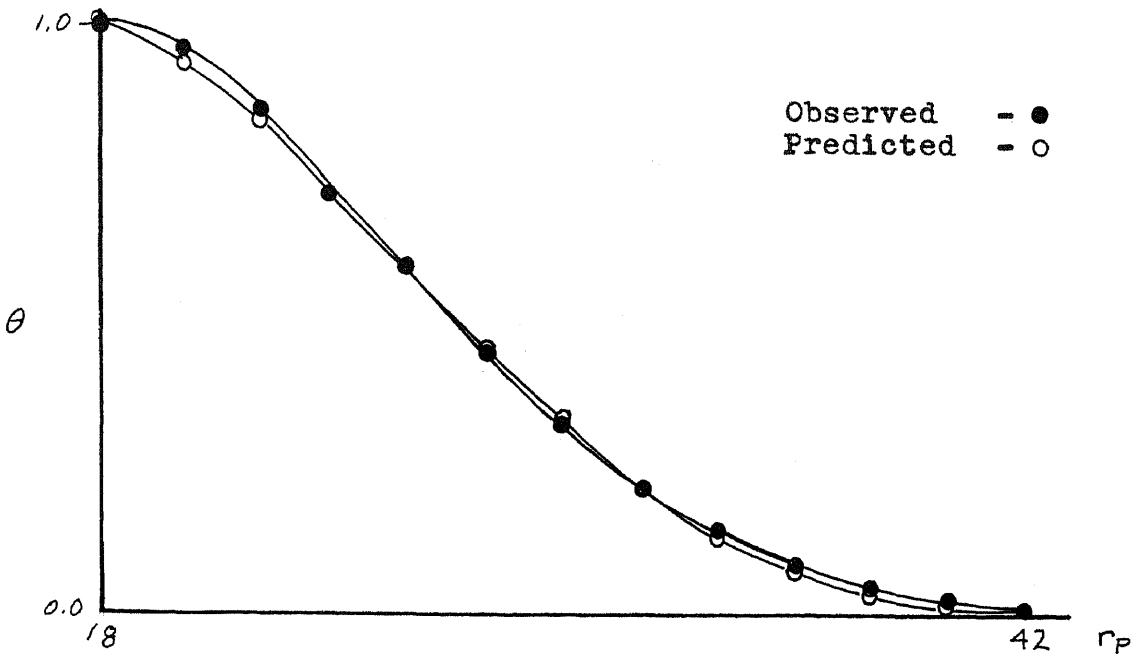

Figure 5.5 - Fractional clearance versus particle radius for dextran under normal hydropenia using the charged case model .

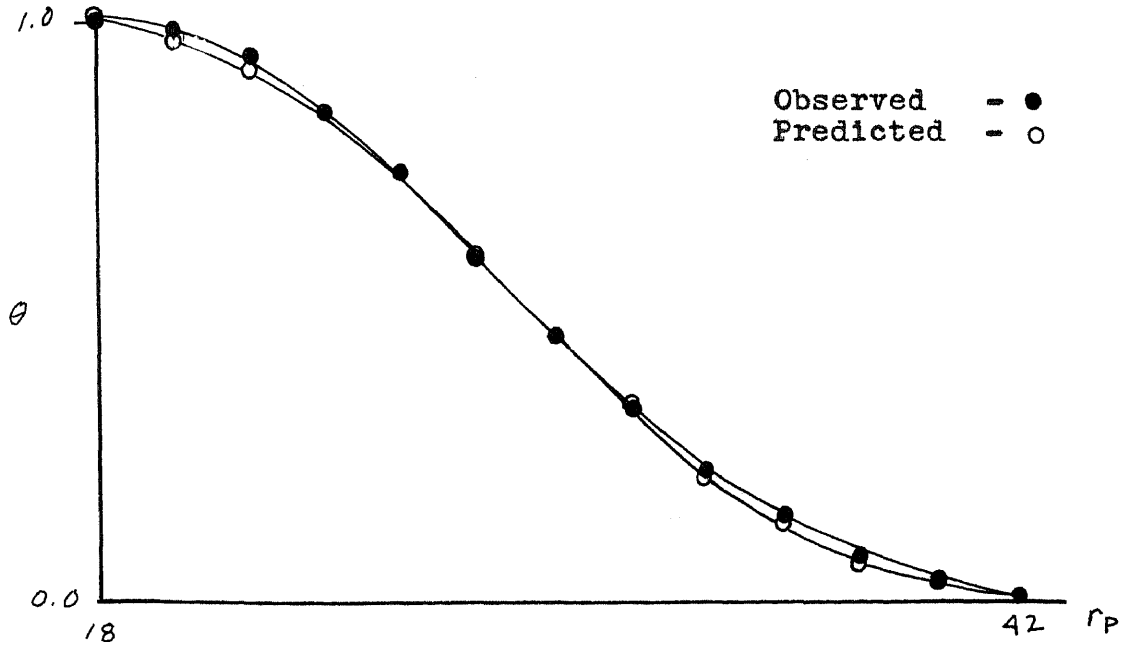

Figure 5.6 - Fractional Clearance versus particle radius for dextran under angiotensin induced conditions using the charged case model.

Table 5.9

Observed and predicted values of fractional clearance versus particle radius for dextran sulfate under normal hydropenia using the charged case model.

Particle Radius r_p (Å)	Observed Fractional Clearance θ_{meas}	Predicted Fractional Clearance θ_{CALC}
18	0.56	0.55
20	0.35	0.36
22	0.19	0.20
24	0.11	0.10
26	0.06	0.04
28	0.032	0.013
30	0.020	0.004
32	0.013	0.0008
34	0.007	0.0002
36	0.003	0.00003
38	0.0009	2.9×10^{-6}
40	0.0004	3.1×10^{-7}
42	0.0002	0.0

Iterated Parameter Estimates

B_1	1.04
B_2	3.50
B_3	2.00
B_4	1.00×10^{3}
B_5	2.00
B_6	0.94
B_7	1.00×10^{-21}
B_8	3.00

Table 5.10

Observed and predicted values of fractional clearance versus particle radius for dextran sulfate under angiotensin induced conditions using the charged case model.

Particle Radius r_p (Å)	Observed Fractional Clearance θ_{meas}	Predicted Fractional Clearance θ_{calc}
18	0.74	0.71
20	0.55	0.56
22	0.37	0.40
24	0.25	0.26
26	0.16	0.14
28	0.099	0.070
30	0.062	0.031
32	0.039	0.011
34	0.021	0.004
36	0.010	1.1×10^{-3}
38	0.0032	2.7×10^{-4}
40	0.0009	5.7×10^{-5}
42	0.0005	1.0×10^{-5}

Iterated Parameter Estimates

B_1	1.12
B_2	2.43×10^{1}
B_3	1.81
B_4	8.16×10^{3}
B_5	1.81
B_6	0.11
B_7	1.08×10^{-20}
B_8	3.00

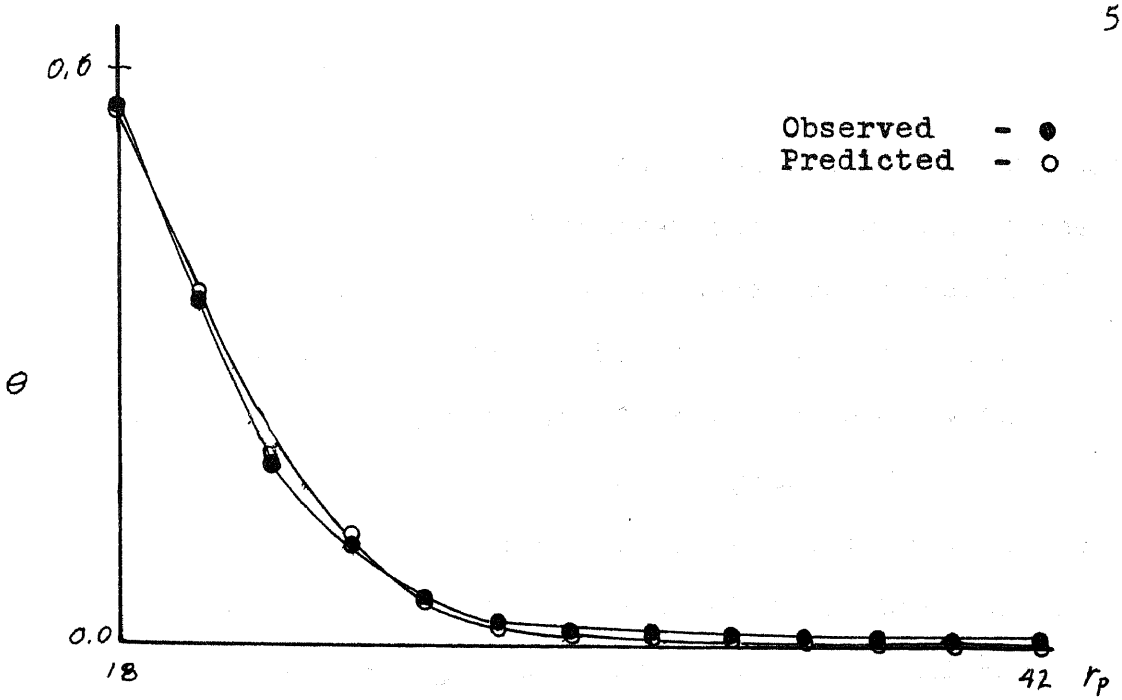

Figure 5.7 - Fractional clearance versus particle radius for dextran sulfate under normal hydropenia using the charge case model .

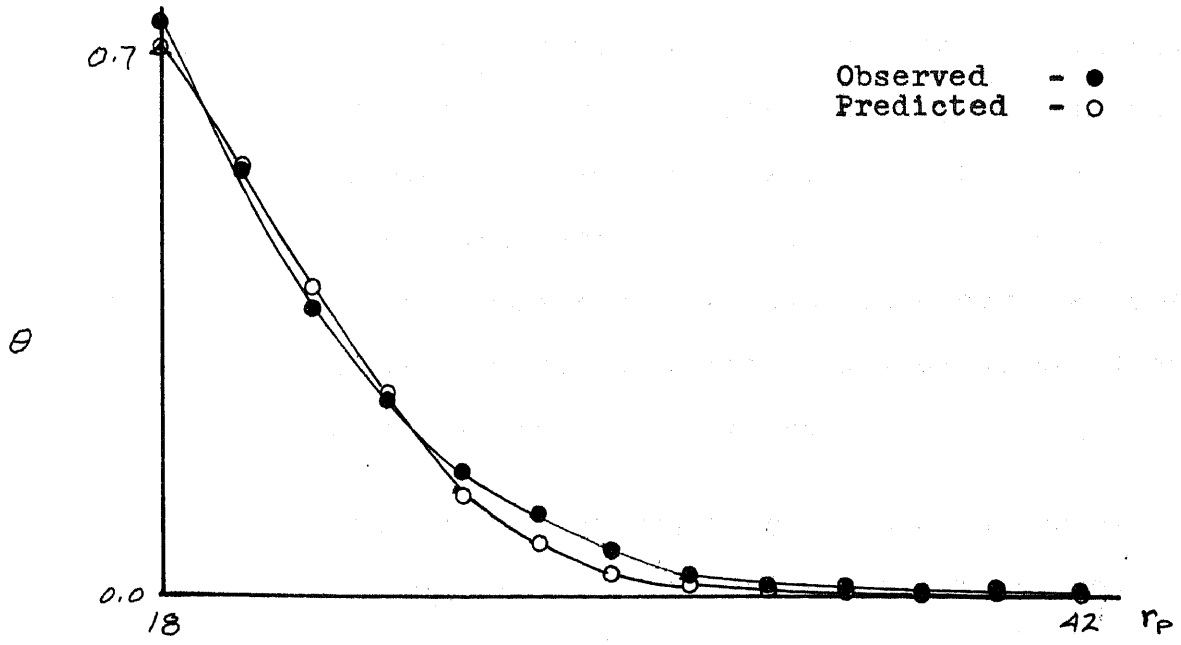

Figure 5.8 - Fractional clearance versus particle radius for dextran sulfate under angiotensin induced conditions using the charged case model.

5.4 Discussion

As seen by the studies presented, use of the uncharged model in the simulation of dextran fractional clearances yielded unfortunate results. In addition to holding n as a constant 2.0 during the fit, other trials were performed with integer value of 1.0 and 3.0 , which resulted in similar poor quality of predicted values. The acquisition of superior results by trials made with the charged case model leads to the conclusion that dextran can not be considered as an electrically neutral macromolecule, but rather has some positive charge associated with its properties.

The curves resulting from the charged case simulation of dextran fractional clearances are comparible to results obtained by the Chang simulation.[1] The results obtained by the simulation of dextran sulfate fractional clearances displayed comparatively less accurate curve fits, particularly the normal hydropenia simulation. The curves, however, are judged reasonable to illustrate certain aspects of the model. In general, Marquardt's method of non-linear least squares proved useful in application.

In the dextran simulation, three of the parameter estimates, B_1 , B_2, and B_6 displayed notable numerical differences in the comparison of the normal hydropenia and angiotensin induced estimates. Since R and L are

considered identical for all cases, B_1 is indicative of the value of $K_P \bar{\nu}_2$, and B_2 of $\bar{\nu}_2$. For both cases, Deen[3] experimentally evaluated the capillary plasma flow rate, Q_A, which was found to be 83.3 nl/min for the normal case, 59.6 nl/min for the angiotensin induced case. For comparison, a ratio of the flow ratesmay be taken, and compared to a simular ratio of the values of B_2 . The experimetal flow rate ratio was found to be 0.72, whereas the predicted ratio was equal to 0.82 . Although numerically imprecise, the model sucessfully illustrates the decreased flow rate induced by the infusion of angiotensin II.

The parameter B_6 is equal to the proportionality constant β , which can be considered indicative of the membrane permeability of a given solute. The increase of β from normal to angiotensin induced studies suggests that angiotensin II increases the permeability of the nephron membrane to dextran.

The dextran sulfate studies are sucessful in showing the charge dependancy of fractional clearance. In both cases, the parameters B_3 and B_5 increased from the corresponding dextran studies. The angiotensin induced study also displays an increase in B4, B_3, B4, and B_5 are all charge related parameters, and an increase of these estimates suggest an increase of the magnitude of the charge attributed to dextran sulfate with respect to dextran.

Unfortunately, the dextran sulfate simulations suffer from ambiguity in estimations of B_2 and B_6 . The normal case shows a increase of flow rate, contradictory to experimental findings. The angiotensin induced simulation arrives at an extreme decrease of flow rate, far exceeding the experimental value. Solute permeability suggested by the two conflict in their estimates. Further investigation into the nature of B_2 and B_6 is suggested.

CHAPTER 6 : CONCLUSION

The investigation performed here has introduced an alternate theory, to elucidate the mass transfer principles governing the nephron and its processes. This analysis shows simple diffusion and electrical forces may be considered to describe the displayed selectivity of the nephron to macromolecules of varying particle radii. Also, a method of non-linear least squares curve fitting has proven successful in obtaining reasonable solutions to this non-linear application.

Further study is suggested with regard to electrical considerations. A more rigorous analysis of the electrical field and its incorporation in the model function is needed. Experimentation is also suggested, in the determination of unavailable parameters.

APPENDIX

Fortran Version of Marquardt's Non-Linear Least Squares Curve Fit Procedure

There is availible a computer version of Marquardt's Non-Linear Least Squares Estimation of Adjustable Parameters, capable of adjusting a maximum of 45 parameters. It is written in Fortran, and in versatile subroutine form.

The program, denoted by the subroutine name NLLSQ, is called by the user's program by the statement

```
CALL NLLSQ ( Y,X,B,RRR,NARRAY,ARRAY,IB )
```

Execution of the program requires definition of the call variables, and the creation of a subroutine named MODEL, which provides the function desired to be fit.

I. Variable Definition

All of the arguements transferred by the CALL NLLSQ statement are arrays, and must contain the following information when the subroutine is called:

Y - contains the values of the dependent variables at the N observed data points.

X - contains the values of the independent variables at the N observed data points. The dimension of X is dependent upon the number of variables specified, M . If M=1, X need only be a singly dimensioned array. For M=2, X must be a two dimensional array, the size of which is at least X(N,M).

B - contains the starting values for the K parameters of the model. At the return of NLLSQ, B contains the final adjusted parameter values.

RRR - an array, whose use is optional, used to communicate between the calling program and the MODEL subroutine. After convergence, all of the residuals may be computed by MODEL, and returned to the calling program via this array.

NARRAY is dimensioned NARRAY(8) and specifies the size

of the problem, and the options desired.

NARRAY(1) - = N, the number of data points to be fitted.

NARRAY(2) - = M, the number of independent variables.

NARRAY(3) - = K, the number of adjustable parameters in the model.

NARRAY(4) - = IP, the number of omitted parameters. An omitted parameter is held constant during the fit.

NARRAY(5) - The size of the intermediate printout after each iteration.

= 0, no intermediate printout.

= 1, prints the current values of the sum of squares PHI, lambda used in the compromise AL, the angle between the correction vector and the negative gradient vector GAMMA, the length of the correction vector in scaled space,XL, the current set of parameters B, and the latest correction vector DB.

= 2, same as 1, and also the parameter correlation matrix.

= 3, same as 2, plus PTP inverse.

NARRAY(6) - The size of the final printout after convergence or force off.

= -1, no output except for error messages.

A force off or the inversion of a singular matrix constitutes an error message.
= 0. prints the output as specified by NARRAY(5) = 3.
= 1, gives, in addition, the observed, predicted, and residual value for each data point, and the one-parameter and support plane confidence region estimates.
= 2, same as above, plus PTP, the PTP correlation coefficients, and the non-linear confidence region calculations.

NARRAY(7) - the output device number. If left 0, the value becomes 06 by default.

NARRAY(8) - KITER, the maximum number of iterations allowed in a fitting. If left 0, the value becomes 30 by default.

ARRAY is an array which contains 8 statistical constants used by NLLSQ. If any of the ARRAY variables are left 0, standand values are provided, as given in Table I . The user need only to specify the nonstandard value he needs.

IB is an integer array, which contains the subscripts of the parameters the user wishes to hold contant. Subsequently, these parameters will not be adjusted from the initial value introduced, and thus the partial derivatives with respect to these parameters are zero, and the PTP matrix contains zeros in the row and column corresponding

to the omitted parameters. The number of omitted parameters are again specified by NARRAY(4).

Table I

Standard values assigned to statistical constants used by NLLSQ when any of the ARRAY variables are left zero.

Program Symbol	Name	Standard Value	Program Use
ARRAY(1)	AL	.1	Inital value of Marquardt's compromise parameter
ARRAY(2)	DELTA	.00001	Increment in forming estimated partials
ARRAY(3)	E	.00005	Epsilon test criterion
ARRAY(4)	FF	4.0	Upper (1-a) point of variance ratio distribution (k,n-k)
ARRAY(5)	GAMCR	45	Critical angle used in GAMMA-EPSILON test
ARRAY(6)	T	2.0	Two tailed (1-a) point of student's t distribution
ARRAY(7)	TAU	.001	Constant used in epsilon test
ARRAY(8)	ZETA	10^{-31}	Singularity criterion in matrix inversion

II. The MODEL Subroutine

The function that is desired to be fit, should be supplied by the user in the MODEL subroutine. The routine provides the service of calculating the function and the residual at each of the N data points. It should also calulate the partial derivatives at each point, if possible. If analytic partials are not availible, MODEL is incorporated in the estimation of the partial values. A COMMON block is used to communicate values between NLLSQ and MODEL.

Proper use of MODEL requires that two statements initiate the routine:

```
SUBROUTINE MODEL ( F,Y,X,RRR,I,JP)
```

and

```
COMMON/BLK1/B(45),P(45),RE,N,M,K
```

The COMMON block transfers the values of the parameters, the partial derivatives, and the residual between routines. The arguements appearing in the MODEL statement enable the transfer of the estimated value of the independent variable F, the observed value Y, the independent variable X, and an optional residual value RRR at the Ith data point. The arguement JP is included for selective computation of varibles by MODEL. If JP = 1, MODEL should only calculate

F and the residual RE. If JP = 2, MODEL should calculate F and RE, and calculate the partial derivatives, or return with JP = 3. The partial derivatives are denoted by P(J), where P is the partial derivative of F with respect to the Jth parameter at the Ith data point. If the partials are not calculated, setting JP= 3 will instruct NLLSQ to numerically estimate P(J). This calculation is accomplished in a subroutine NEWA, which is provided in NNLSQ. An incremental technique is used in partial estimation, the value of the increment given by ARRAY(2) . Setting JP = 4 allows the option of the user to calculate F and RRR(I) after convergence, where RRR may, for instance, calculate the value of the residual at the Ith data point.

For illustration purposes, the following function is considered:

$$f(x) = B_1 x + B_2 e^{-B_3 x}$$

where f is the function to be fitted to the data, x the independent variable, and B_1, B_2, and B_3 are the adjustable parameters. In this case M = 1 and K = 3. It is assumed that 15 data points are available, and therefore N = 15. Analytic partial derivatives are easily found and therefore

$$p_1 = \frac{\partial f}{\partial B_1} = x$$

$$p_2 = \frac{\partial f}{\partial B_2} = e^{-B_3 x}$$

and

$$P_3 = \frac{\partial f}{\partial B_3} = -B_2 X e^{-B_3 X}$$

The MODEL would appear as follows:

```
      SUBROUTINE MODEL ( F,Y,X,RRR,I,JP )
      COMMON/BLK1/B(45),P(45),RE N,M,K
      DIMENSION Y(15),X(15)
      F = B(1)*X(I) + B(2)*EXP(-B(3)*X(I))
      RE = Y(I) - F
      GO TO ( 30,10,30,20 ), JP
10    P(1) = X(I)
      P(2) = EXP(-B(3)*X(I))
      P(3) = -B(2)*X(I)*P(2)
      RETURN
20    RRR(I) = RE
30    RETURN
      END
```

III. Comments

Because of it's subroutine form, NLLSQ (Non-Linear Least SQuares fitting routine) may be incorporated in in any number of applications, as the sole calculation, or the part of a larger program. Of course, computation time should be considered in the implementation of NLLSQ.

When convergence of a solution is reached, the routine outputs this information. Failure to converge within the specified number of iterations will result in a FORCE OFF message, and control will return from NLLSQ. Care should be taken in the initial estimates of the parameters, otherwise a false convergence or FORCE OFF will occur. Poor inital estimates may also result in computer computation difficulty.

If weighting of the residual function is desired, simple modification of the MODEL subroutine is only necessary. If in the example given (p. 61) it is desired to weight the residual by the inverse of the observed dependent varible, RE would be calculated in the routine as

```
RE = (1.0/Y(I))*( Y(I) - F )
```

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