CHAPTER V

A MATHEMATICAL MODEL OF THE TRANSIENT DIFFUSION OF FLUORESCIN ACROSS THE BLOOD-RETINA-BARRIER
5.1 INTRODUCTION

The transport of nutritional substances as well as the injected tracers occurs due to the convection, active transport and vesicular transport from the blood into the tissue spaces and vice-versa. A structure which prevents the normal diffusion from the one space to other causing disturbance in the transport mechanism is called a Barrier.

The blood-retina barrier separates the retinal cells from the blood stream. It is constituted by endothelial lining of retinal vasculature and pigment epithelium. The blood-retina barrier is tight and it allows the passage of only a few important substances (e.g. Glucose, Sucrose and certain amino acids etc.) from the blood into the vitreous body while all other substances are retained. The detailed description of the blood-retina barrier has been given in Chapter 1.

The abnormal functioning of blood-retina barrier is one of the responsible factors for the development of a number of ocular diseases and macular pathology [Cunha-Vaz (1980)]. In the abnormal circumstances of blood-retina barrier, the permeability of blood-retina barrier is altered causing the passage of other substances (normally not allowed to pass across) which disturbs the retinal homeostasis leading to certain diseases e.g. vascular retinopathy, pigment epitheliopathy and renal edema etc., resulting in disturbance in the visual acuity, in severe cases, to blindness.
The permeability of the blood-retina barrier can be defined as a microscopic measure of its facility to penetration of certain substances through it. An exact determination of the permeability may provide a deeper and more viable understanding of pathophysiology of the disease which is associated with barrier-breakdown. Also, the permeability may be a sensitive parameter for the assessment of certain disease and its intensity. Also, the permeability of the blood-retina barrier is suitable for the mathematical analysis. Thus, the mathematical analysis of the transport phenomenon and behaviour of the blood-retina barrier towards it, in the normal as well the diseased state may prove useful for clinical significance.

In a method of measuring the penetration through the blood-retina barrier into the blood stream the water soluble substance fluorescein (mol. wt = 372, r = 5.5 Å) is injected into the midvitreous. This special marker for the retinal circulation and the blood-retina barrier fluorescein has been used since 1980 [Araie, Sawa Naataki et al (1980)]. Since the injected fluorescein is continuously eliminated from the vitreous body into the blood stream across the blood-retina barrier, the transport problem is transient. The time history of the fluorescein concentration in the vitreous body together with a parameter describing the permeation across the blood-retina barrier into the blood and permeability coefficient and diffusion coefficient in the vitreous body suffice to determine the concentration of
fluorescein in the vitreous body. Cunha-Vaz and Maurice (1967) presented a mathematical model to calculate the permeability of blood-retina barrier using Crank's solutions for constant fluid (1956). For approximate value of the permeability of the barrier, Lund-Anderson and Larsen (1981) normalized the area below the concentration profile in the vitreous with the area below the time history of fluorescein concentration in the blood plasma. Krogsaa et al (1981, 1983) have given a good review on the subject. However, Krogsaa et al presented the mathematical analysis only for intraperitoneal diffusion of tracer.

The present study deals with the mathematical analysis of fluorescein in the vitreous body and the subsequent transport across the blood-retina barrier in transient state. The velocity of the liquid is obtained from Brinkman's equation. This velocity is used as convective velocity in the diffusion equation. The differential equation is solved by Galerkin technique [Hildebran (1968)] using Laplace transformation [Snedon (1974)]. The effect of the permeability as a sensitive parameter characterising the physiological function of the blood-retina barrier on the fluorescein transport is studied.

5.2 FORMULATION OF THE PROBLEM

As discussed in Chapters I and IV that the vitreous body consists a loosely packed fibrous frame work of collagenous fibrous covered with a homogeneous membrane
which is made up of collagen like fibres. The vitreous chamber has a pore like structure filled with vitreous humour with hypothetical source cavity. We assume that this cavity originates the moving liquid and the tracer is injected in the cavity. Jakson et al (1982) suggested that flow of liquid through the vitreous body can be described by Darcy's law [Darcy (1856)]. Darcy's law is applicable only to the porous system having large permeability. The permeability of the vitreous is very small. Thus, the fluid velocity through the vitreous body can be described by Brinkman's equation [Brinkman (1947)]. Basically, the composition of vitreous humour and aqueous humour are same. We assume, therefore, vitreous body is filled with the aqueous humour.

We assume that the vitreous body has a homogeneous and isotropic structure with incompressible fluid. Therefore, Equation (1.12) and (1.20) reduce to the following equations (Fig. 5.1):

\[
\frac{\mu}{r^2} \frac{\partial V}{\partial r} \left( r^2 \frac{\partial V}{\partial r} \right) - \frac{\mu}{K_V} V = \Delta P \tag{5.1}
\]

\[
\frac{\partial}{\partial t} \frac{\partial C_{IV}}{\partial r} + V \frac{\partial C_{IV}}{\partial r} = \frac{D}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial C_{IV}}{\partial r} \right) \tag{5.2}
\]

Now, the problem is to solve the above equations (5.1) and (5.2) subject to the following conditions:

\[
C_{IV} (r, 0) = 0 \tag{5.3}
\]

\[
v_V(a) = v_V^0 \tag{5.4}
\]
Fig. 5.1 A simplified model of blood-retina barrier in the eye.
\[
\frac{\partial \nu_V}{\partial r} \bigg|_{r=0} = 0 \tag{5.5}
\]

\[
\frac{\partial C_{IV}}{\partial r} \bigg|_{r=0} = 0 \tag{5.6}
\]

\[
\frac{\partial C_{IV}}{\partial r} \bigg|_{r=a} = \frac{p^0_{IV}}{D_f} [C_{IV}(a,t) - C_{IV}(t)] \tag{5.7}
\]

where \( C_{IV}^p(t) \) is the concentration of fluorescein in the blood plasma. It is assumed that it decays according to the form:

\[
C_{IV}^p(t) = C_{IV}^p(1 - e^{-n_3 t}) \tag{5.8}
\]

in which \( n_3 \) is the decay constant. The barrier condition is found by the assumption that the flux across the barrier is proportional to the difference in concentrations on either sides of the barrier. \( P_{IV} \) is the permeability coefficient per unit area of the retina-vitreous interface.

The diffusive flux and convective flux of fluorescein in the vitreous body are given by the equations:

\[
J_{V\text{diff}} = -D_f \text{grad} C_{IV} \tag{5.9}
\]

\[
J_{V\text{conv}} = v_V C_{IV} \tag{5.10}
\]

5.3 SOLUTION TO THE PROBLEM

The solution of Equation (5.1) has been obtained as follows:
Substituting this expression in equation (5.2) and taking Laplace transform of resulting equation and prescribed boundary condition, we obtain:

\[ \frac{1}{D_F} \bar{C}_{IV} = \frac{a^2 \bar{C}_{IV}}{a r^2} + \left[ \frac{2}{r} - i (v_0^o + \frac{K_v \Delta P}{\mu}) \frac{a}{\text{Sinh} \frac{1}{K} a} \right] \frac{\text{Sinh} \frac{1}{K} r}{r} - \frac{K \Delta P}{\mu} \]  

(5.12)

\[ \frac{\partial \bar{C}_{IV}}{\partial r} \bigg|_{r=0} = 0 \]

\[ \frac{\partial \bar{C}_{IV}}{\partial r} \bigg|_{r=a} = \frac{P^o_{IV}}{D_F} \left[ \bar{C}_{IV}(a, s) - C^p_{IV}(s) \right] \]  

(5.13)

The solution of transformed equation (5.12) for \( \bar{C}_{IV} \) is obtained by the Galerkin technique. We assume a trial function for \( \bar{C}_{IV} \) as given below:

\[ \bar{C}_{IV} = \frac{-P^o_{IV} C_p(s)}{(2aD_F + p^o_{IV} a^2)} - \sum_{i=1}^{2} A_i (r-a)^2 \cdot r^{2i} \]  

(5.14)

We obtain the expressions of \( A_1 \) and \( A_2 \) by substituting this expression in equation (5.12) and minimizing the residual by Galerkin method, we get...
\[ \int_0^a R (r-a)^2 r^2 \, dr = 0 \quad \text{(5.15)} \]

\[ \int_0^a R (r-a)^2 r^4 \, dr = 0 \quad \text{(5.16)} \]

\[
A_1 = -p_{IV}^0 \frac{\overline{c}_p (s)}{2aD_f + p_{IV}^o a^2} \left[ \frac{s^2 - K_1 s + K_2}{s^2 - K_3 s + K_4} \right] \quad \text{(5.17)}
\]

\[
A_2 = -p_{IV}^0 \frac{\overline{c}_p (s)}{2aD_f + p_{IV}^o a} \left[ \frac{s^2 - K_5 s + K_6}{s^2 - K_3 s + K_4} \right] \quad \text{(5.17)}
\]

\[
\overline{c}_p (s) = \left( \frac{1}{s} - \frac{1}{s+n} \right) \overline{c}_{IV}^p \quad \text{(5.19)}
\]

\[
\overline{c}_{IV} = -p_{IV}^0 \left[ \frac{1}{s} - \frac{1}{s+n} \right] \frac{\overline{c}_p}{2aD_f + p_{IV}^o a^2}
\]

\[
+ A_1 \frac{L_4 L_{12} - L_6 L_{10}}{L_2 L_{10} - L_4 L_8} (r^4 + a^2 r^2 - 2a r^3)
\]

\[
+ A_2 \frac{L_6 L_8 - L_2 L_{12}}{L_2 L_{10} - L_4 L_8} (r^6 + a^2 r^4 - 2a r^5) \quad \text{(5.20)}
\]

Taking inverse Laplace transform of equation (5.20), we obtain
\[ C_{IV} = \frac{P(1 - e^{-3}) C_{IV}}{a(2D + P \alpha)} r^2 + \frac{C_{IV} P_{IV}}{a(2D + P \alpha)} \times \frac{L_{6} L_{10} - L_{4} L_{12}}{L_{2} L_{10} - L_{4} L_{8}} x \]

\[ (r^4 - 2ar^3 + a^2 r^2) \times [1 - \frac{2(K_1 - K_3)}{(M_1 - M_2)M_1} x \]

\[ (1 - e_{M_1} t) - \frac{K_4 - K_2 - M_2(K_1 - K_3)}{(M_1 - M_2)M_2} (1 - e_{M_2} t) \]

\[ -e_{M_1}^3 \{ 1 - \frac{(K_1 - K_3)M_1 - M_4 + K_2}{(M_1 - n_3)(M_1 - M_2)} - \frac{K_4 - K_2 - M_2(K_1 - K_3)}{(M_1 - M_2)(M_2 - n_3)} \} \]

\[ -\frac{(K_1 - K_3)M_1 - K_4 + K_2}{(M_1 - M_2)(M_1 - n_3)} e^{-M_1 t} \]

\[ \frac{C_{IV} P_{IV}}{a(2D + P \alpha)} \times \frac{L_{6} L_{12} - L_{4} L_{8}}{L_{2} L_{10} - L_{4} L_{8}} x \]

\[ (r^6 + 2ar^4 + a^2 r^2) \times \]

\[ [1 - \frac{(K_5 - K_3)M_1 - K_6 + K_2}{(M_1 - M_2)} \{ \frac{1 - e^{-M_1 t}}{M_1} + \frac{e^{-M_1 t}}{M_1 - n_3} \} \]

\[ \frac{K_6 - K_2 - M_2(K_5 - K_3)}{M_1 - M_2} \{ \frac{1 - e^{-M_2 t}}{M_2} + \frac{e^{-M_2 t}}{M_1 - n_3} \} \]

\[ -e_{M_1}^3 (1 - \frac{(K_5 - K_3)M_1 - K_6 + K_2}{(M_1 - M_2)(M_1 - n_3)} - \frac{K_6 - K_2 - M_2(K_5 - K_3)}{(M_1 - M_2)(M_2 - n_3)} \]
\[ K_1 = \frac{L_{12}L_{13} + L_{11}L_4 - (L_5L_6 + L_5L_{10})}{L_4L_{12} - L_6L_{10}} D_f \quad (5.22) \]

\[ K_2 = \frac{L_{11}L_3 - L_5L_9}{L_4L_{12} - L_6L_{10}} D_f^2 \quad (5.23) \]

\[ K_3 = \frac{L_{11}L_9 + L_2L_9 - L_3L_8 - L_4L_7}{L_2L_{10} - L_4L_8} D_f \quad (5.24) \]

\[ K_4 = \frac{L_1L_9 - L_3L_9}{(L_2L_{10} - L_4L_8)} D_f^2 \quad (5.25) \]

\[ K_5 = \frac{L_6L_7 + L_5L_8 - L_{11}L_2 - L_{12}L_1}{L_6L_8 - L_{12}L_2} D_f \quad (5.26) \]

\[ K_6 = \frac{(L_5L_7 - L_1L_{11}) D_f^2}{(L_6L_8 - L_{12}L_2)} \quad (5.27) \]

\[ M_1 = \frac{K_3 + \sqrt{K_3^2 - 4K_4}}{2} \quad (5.28) \]

\[ M_2 = \frac{K_3 + \sqrt{K_3^2 - 4K_4}}{2} \quad (5.29) \]

\[ L_1 = -0.03412556 - \frac{1}{D_f} (v_v^0 + \frac{K\Delta P}{\mu}) \frac{a(v_K)^5}{\sinh^{\frac{1}{K}}_1 a} \left\{ 60(v_K)^2 \cosh^{\frac{1}{K}}_1 a \right. \\
+ \cosh^{\frac{1}{K}}_1 a - 15v_K \sinh^{\frac{1}{K}}_1 a \} \quad (5.30) \]

\[ L_2 = -0.54464347 \quad (5.31) \]

\[ L_3 = 0.081901264 \frac{1}{D_f} (v_v^0 + \frac{K\Delta P}{\mu}) \frac{720a}{\sinh^{\frac{1}{K}}_1 a} \left\{ 125(v_K)^9 \cosh^{\frac{1}{K}}_1 a \\
+ 2a(v_K)^7 \cosh^{\frac{1}{K}}_1 a + 1.2v_K \sinh^{\frac{1}{K}}_1 a \right\} \]
\[ L_4 = 3.308916 \times 10^{-3} \quad (5.32) \]
\[ L_5 = 0.331776 + 0.0497664 \cdot \frac{K_{VP}}{\mu} - \frac{24}{D_f} \left( v^0 V + \frac{K_{VP}}{\mu} \right) a(vK_V) \frac{5}{1} \frac{\cosh \frac{1}{K_V}}{a} \quad (5.33) \]
\[ L_6 = 0.03412553 \quad (5.34) \]

Computational results obtained by using the values of model parameters for human eye have been presented through the curves plotted in Figures 5.2 - 5.4 in the following section.

5.4 RESULTS AND DISCUSSION

Figure 5.2 is the schematic representation of the concentration profiles of intravitreally injected fluorescein in the vitreous body of the eye at 30, 60 and 120 minutes after the injection. The effect of permeability coefficient of the blood-retina barrier on the concentration-distribution also have been brought out. It is clear from these graphs that there is continuous decrease in the concentration along the radial direction far away from the hypothetical cavity. With the passage of time after the injection, concentration goes on increasing at a particular point. Also, it is observed from the graphs that as the permeability is increased, there is a remarkable change in the concentration.
Fig 5.2 Concentration profiles for different values of the permeability coefficient for $D = 6E-6 \text{ cm}^2/\text{sec}$
In Figure (5.3), we have shown the effect of the diffusion coefficient on the fluorescein diffusion in the vitreous body at a specified region at 30, 60 and 120 min after the injection from the graphs, we observe that with the passage of time, the fraction of mass in increases with increase in the diffusion coefficient.

In Figure (5.4), the concentration-distribution of fluorescein in the vitreous body has been represented by graphs. The continuous line shows the concentration distribution of fluorescein carried by the bulk flow in the vitreous body and the dotted line represents the concentration-distribution of diffusive flux of the tracer. The effects of the permeability coefficient of the blood-retina barrier, in normal and pathological states of the retina, on the bulk diffusion and diffusive flux have been displayed. In case of retinal holes or retinal detachment, the loss of fluorescein through the blood-retina barrier is increased due to increased bulk flow through retinal holes. Also, in the above case, permeability of blood-retina barrier increases. It was shown by the Cantrill et al in 1984 that the disappearance of fluorescein was increased to about 5% with the increase of two and half times in permeability. It seems that it contributes mainly to the fast movement of the tracer. Thus, increasing permeability of blood-retina barrier causes an increase in the concentration-distribution due to bulk flow
Fig. 5.3 Variation of fluorescein fraction at \( r = 0.6 \text{ cm} \) with diffusion coefficient at different times after injection.
Fig. 5.4 Variation of convective and diffusive fluxes for different values of permeability
as demonstrated by the graphs.

Also, the graphs show slight increase in the diffusive-flux concentration distribution of the tracer with increase in permeability of the blood-retina barrier.