CHAPTER VI

SOLUTE TRANSPORT IN THE PRODUCTION OF CEREBROSPINAL FLUID
7.1 INTRODUCTION

From strictly morphological considerations, the choroid plexuses have long been implicated as a major source of cerebrospinal fluid production. During the last two decades anatomical speculation regarding the role of the plexuses in the production of cerebrospinal fluid has been confirmed. Although the estimates of the total production of cerebrospinal fluid by the choroid plexuses is difficult, Welch (1963) and Davson and Segal (1970) have argued that plexuses produce about 70-80% of the cerebrospinal fluid through the secretion process. It was later on suggested by McComb (1983) that in normal subjects about 80% to 90% of cerebrospinal fluid secretion is derived from the choroid plexuses. The remaining portion most likely originates from the parenchyma. Thus, most of cerebrospinal fluid is formed in the ventricular system from the choroid plexuses.

The choroid plexuses are delicate frond-like gel structure which floats in the cerebrospinal fluid. Morphologically, as with other more familiar fluids transporting epithelia (gall bladder, renal tubule, ciliary process etc), the choroid plexuses are characterised by a rich capillary bed closely opposed to a single layer of epithelial cells folded into numerous small villi. The tight junctions are attached at the apical sides of the cells and present, the blood-cerebrospinal fluid barrier. Ultrastructural modifications of the choroid ependymal cell membrane into
infoldings and apical microvilli also exhibit characteristics of epithelia that transport the fluid.

To investigate the mechanism by which an epithelium transports a fluid, it is necessary to understand the properties of the epithelia and factors upon which the fluid production is dependent. The factors upon which the secretion of cerebrospinal fluid is dependent have not been clearly specified in the available literature. This is probably due to structural complexity of the tissue of the choroid plexuses. The formation of cerebrospinal fluid in the ventricular cavities derives from the transepithelial transport of solutes and solvent like other fluid transporting epithelia. Epithelial membranes have the ability to transport water and solute between serosal and mucosal solutions which are either isotonic or have hydrostatic and electrochemical gradients counter to the direction of flow. This supports the concept of an osmotic movement of water possibly linked with the movement of sodium. Wright (1972) and Segal and Pollay (1971) have demonstrated a net flux of sodium from blood to cerebrospinal fluid.

Diamond and Bossert's (1967) standing gradient model has played an important role in modelling the transport of solutes across a variety of epithelia which absorb or secrete fluids. A generalization of different boundary conditions has been given by Sackin and Boulpaep (1975) for
single solute transport whereas the case of two solutes has been considered by Andrietti et al (1979, 1982). The original non-linear model is not suitable to analytical treatment due to mathematical complexity, some considerations on the qualitative behaviour of the solutions, their existence and uniqueness have been given by Sackin and Boulpaep (1975) and Garner and Kellog (1980). On the other hand, Segal (1970) has provided a linear approximation, the so-called isotonic convection approximation which permits to treat the problem analytically. This approximation has been used by many authors interested in the analysis of water and solutes transport in epithelia [Hill (1975), King-Hele (1977), Weinstein and Stephenson (1981) and Andertti (1986)].

An important aspect of current models of coupled salt and water transport concerns the direction of fluid transport within fluid transporting intercellular cleft. In most tissues, the proposed direction of flow is towards the open end of the clefts. This direction has been termed as "Forwards" by Diamond and Bossert (1968). In the choroid plexus, as well as in few other tissues, flow is to be in the "Backwards" direction. Diamond and Bossert (1968) proposed that salt is transported out of the intercellular clefts in the regions close to tight junctions causing a local increase in osmotic pressure within the cell and water is withdrawn out of the cleft. The movements of water and salt would, in turn, draw more fluid down the cleft,
setting up a reverse osmotic gradient. Using Diamond and Bossert's "standing gradient" hypothesis, Segal and Pollay (1971) proposed that Na/K-ATPase pumps sodium into the basal side of the cell, with water entering by the osmotic gradient created. Chloride may be coupled with this process or may enter the cell separately. Na/K ATPse located in the microvilli on the apical surface extrudes sodium from the cell with osmotic movement of water into the ventricle.

In this chapter, we extend Diamond and Bossert's model for two dimensional form to describe the transport of solutes and water across the choroid plexuses considering both ends of the cleft open. Also, the role of a leaky tight junction in epithelia is examined by considering the flow of water and solute through a channel consisting of two sections representing the extracellular space and tight junction using a single pore model and isotonic convection approximation. We shall examine the flow produced by imposed concentration and pressure differences as well as by active transport into the intercellular space. In this model, the solution depends upon the geometrical properties of tight junction.

7.2 FORMULATION OF THE PROBLEM

Consider an electroneutral channel consisting of two sections: an extracellular channel, \( 0 \leq x \leq L_1 \) and a tight junction, \( L_1 \leq x \leq L_2 + L_1 \) (Fig. 8.1). The fluid in the channel is assumed to be two-species continuum
Fig. 7.1 A simplified model of extracellular channel with tight junction of choroid plexus.
a solute and water. It is assumed that both ends \( x = 0 \) and \( x = L_2 + L_1 \) are open and lateral cell membranes of the extracellular channel allow passive leak of water and solute through itself. Fluid enters the channel at end \( x = 0 \). Most of the solute in the channel is transported out of the channel by active pump located at the lateral walls of the extracellular channel followed by passive movement of water with solute. Some amount of fluid passes through the tight junction to reach the ventricular space directly. We assume that all actively transported solute, passively transported solute and water reach the ventricular space.

The governing equation of continuity may be written as given below:

\[
\frac{\partial u_{CF}}{\partial x} + \frac{\partial w_{CF}}{\partial y} = 0 \tag{7.1}
\]

and the diffusion equation is

\[
D_{CF} \nabla^2 C_{CF} = u \frac{\partial C_{CF}}{\partial x} + w \frac{\partial C_{CF}}{\partial y} \tag{7.2}
\]

Boundary and Barrier conditions:

\[
D_{CF} \frac{\partial C_{CF}}{\partial y} \bigg|_{y=h} = N + p_s^C \left(C_{CF} - C_{CF}'\right); \quad 0 \leq x \leq L_1 \tag{7.3}
\]

\[
= 0; \quad L_1 \leq x \leq L_1 + L_2 \tag{7.4}
\]
\[
\frac{\partial C_{CF}}{\partial y} \bigg|_{y=0} = 0 \quad (7.5)
\]

\[W_{CF} (x, 0) = 0 \quad (7.6)\]

\[W_{CF} (x, h) = P_{CF}^{W} (C_{CF} - C_{CF}') \quad 0 \leq x \leq L_1 \quad (7.7)\]

\[= 0 \quad L \leq x \leq L_1 + L_2 \quad (7.8)\]

\[c(0, y) = c_{CF}^{+} \Delta C_{CF} \quad (7.9)\]

\[c(L_1 + L_2, y) = c_{CF}^{+} \quad (7.10)\]

\[P(0) = P_0 + \Delta P, \quad P(L_1 + L_2) = P_0 \]

By integrating equations (7.1) and (7.2) with respect to \(y\) between 0 to \(h\) due to symmetry

\[\frac{\partial}{\partial x} (u_{CF}' C_{CF}) - D_{CF} \frac{\partial^2 C_{CF}}{\partial x^2} = N - \frac{P_{CF}^s (C_{CF} - C_{CF}')}{\partial x} - P_{CF}^{W} (C_{CF} - C_{CF}')C_{CF} \quad (7.11)\]

\[0 \leq x \leq L_1 \]

\[\frac{\partial}{\partial x} (u_{CF}' C_{CF}) - D_{CF} h_2 \frac{\partial^2 C_{CF}}{\partial x^2} = 0 \quad L_1 \leq x \leq L_1 + L_2 \quad (7.12)\]

\[\frac{\partial u_{CF}'}{\partial x} = -P_{CF}^{W} (C_{CF} - C_{CF}') \quad 0 \leq x \leq L_1 \quad (7.13)\]

\[= 0 \quad L_1 \leq x \leq L_1 + L_2 \quad (7.14)\]

in which

\[u^* = \int_{0}^{h} u \, dy \quad (7.15)\]
Flow through the intercellular space is typically very slow and consequently there is a balance between the viscous forces and pressure gradient forces at each section. We assume that Poiseuille flow holds locally at each section so that

$$u^*_{CF} = \frac{-h^3}{12 \mu} \frac{dp_{CF}}{dx}$$  \hspace{1cm} (7.16)

### 7.3 SOLUTION TO THE PROBLEM

(a) Analytical Solution:

For mathematical tractability, we assume N to be constant. Further from equations (7.11) - (7.14) using isotonic convection approximation, we obtain following governing equations

\[
\frac{\partial}{\partial x} \left[ \left( \frac{p^s_{CF}}{p^w_{CF}} - 2c'_{CF} \right) u^*_{CF} - D_{CF} h_1 \frac{\partial^2 u^*_{CF}}{\partial x^2} \right] = -N_{CF} \quad 0 \leq x \leq L_1 \\
D_{CF} h_2 \frac{\partial^2 u^*_{CF}}{\partial x^2} = 0 \quad L_1 \leq x \leq L_1 + L_2 \quad (7.17)
\]

Integrating equation (7.17) with respect to x we obtain,

\[
\left( \frac{p^s_{CF}}{p^w_{CF}} - 2c'_{CF} \right) u^*_{CF} - D_{CF} h_1 \frac{2u^*_{CF}}{x^2} = -N_{CF} x + S \quad (7.19)
\]

Let $u_0$ be a representative, value of volume flux. Define non-dimensional variables by
\[ \bar{x} = \frac{x}{L_1}, \bar{h} = \frac{h_2}{h_1}, \bar{L} = \frac{L_2}{L_1}, \bar{u}_{CF} = \frac{u_{CF}}{u_0} \]

\[ \bar{c}_{CF} = \frac{(C_{CF} - C_1) p_{CF}^{w} L_1}{u_0}, \bar{P}_{CF} = \frac{(P_{CF} - P_0)}{12 \mu L_1 u_0} h_1^3 \] (7.20)

Equations (7.13), (7.14), (7.16), (7.18) become

\[ \frac{\partial^2 \bar{u}_{CF}}{\partial x^2} - k_1^2 \bar{u}_{CF} = -n \bar{x} + S_1 \quad 0 \leq x \leq 1 \] (7.21)

\[ \frac{\partial \bar{u}}{\partial x} = 0 \quad 1 \leq x \leq 1 + 1 \] (7.22)

\[ \frac{\partial \bar{c}}{\partial x} = 0 \quad 1 \leq x \leq 1 + 1 \] (7.23)

\[ \bar{c} = - \frac{\partial \bar{u}}{\partial x} \quad 0 \leq x \leq 1 \] (7.24)

\[ \bar{u} = - \frac{\partial \bar{c}}{\partial x} \quad 0 \leq x \leq 1 \] (7.25)

\[ \bar{u} = -h_1^3 \frac{\partial \bar{P}}{\partial x} \quad 0 \leq x \leq 1 + 1 \] (7.26)

Dimensionless boundary conditions are:

\[ \bar{c}_{CF}(0) = \frac{\Delta C_{CF} p_{CF}^{w} L_1}{u_0} = \bar{C}_{CF} \] (7.27)

\[ \bar{c}_{CF}(1+1) = 0 \] (7.28)

\[ \bar{P}_{CF}(0) = \frac{\Delta \bar{P}_{CF} h_1^3}{12 \mu L_1 u_0} \] (7.29)
\[ p_{CF}(1+1) = 0 \] 

where

\[ k_1^2 = \frac{p_s^{CF}}{p_{CF}^{CF}} - 2 c_{CF}' L_1^2 \frac{p_w}{D_{CF}^2 h_1} \]  

(7.31)

\[ n = - \frac{N L_1^3}{D_{CF}^2 h_1 u_0} \]  

(7.32)

\[ S_1 = - \frac{S L_1^2}{D_{CF}^2 h_1 u_0^2} \]  

(7.33)

Differential equations (7.21) - (7.26) can be solved by using the set of boundary conditions (7.27) - (7.30) under the assumption that the flow and concentration are continuous at \( \bar{x} = 1 \)

\[ \bar{c}_{CF} = \frac{\Delta c_{CF}}{u_0} \frac{P_{CF}^{CF} L_1}{1} \left[ \cosh k_1 \bar{x} - \frac{k_1 \sinh k_1 + h \cosh k_1}{k_1 \cosh k_1 + h \sinh k_1} k_1 \sinh k_1 \bar{x} \right] \]

\[ + \frac{n}{k_1^2} \left[ 1 - \cosh k_1 \bar{x} - \frac{k_1 \sinh k_1 - h(1 - \cosh k_1)}{k_1 \cosh k_1 + h \sinh k_1} k_1 \sinh k_1 \bar{x} \right] \]

\[ 0 \leq \bar{x} \leq 1 \]  

(7.34)

\[ \bar{u}_{CF} = \frac{\Delta c_{CF}}{u_0} \frac{P_{CF}^{CF} L_1}{1} \left[ \cosh k_1 \bar{x} - \frac{\sinh k_1 \bar{x}}{k_1} \right] \]
The pressure \( P \) can be found from equations (7.25) and (7.26) in terms of the constant \( S_1 \) and the conditions (7.29 - 7.30) is satisfied, if

\[
\int_0^1 \bar{u}_{CF} \, d\bar{x} + \int_{1}^{1+1} \bar{u}_{CF} \, d\bar{x} = -\frac{\Delta \bar{P}_{CF}}{12u_0} h^3
\] 

This determines the constant \( S_1 \), giving
\[ S_1 = \frac{k_1^2}{(1+1/h^3)} \left[ \frac{\Delta P_{CF}}{12\mu L_1 u_0} \frac{h^3}{12\mu L_1 u_0} + \frac{\Delta C_{CF}}{h^3} \left\{ \frac{k_1 L\text{Sinh}k_1 - h(1-\text{Cosh}k_1)}{k_1 L\text{Cosh}k_1 + h\text{Sinh}k_1} \right\} \right] \]

\[ + \frac{h^2}{k_1^2} \left[ 1 + \frac{1}{h^3} - \frac{1}{h^3} \left( \frac{1}{k_1} \frac{\text{Sinh}k_1}{\text{Cosh}k_1} - \text{Cosh}k_1 + 1 \right) \right] \]

\[ - \frac{k_1 L\text{Sinh}k_1 + h\text{Cosh}k_1}{k_1 L\text{Cosh}k_1 + h\text{Sinh}k_1} \left( \frac{\text{Sinh}k_1}{h^3} + \frac{L\text{Cosh}k_1}{k_1} \right) \] (7.39)

(b) Numerical Solution

In order to obtain numerical solution of nonlinear equations (7.11) and (7.12), we eliminated \( u_{CF}^* \) from equations (7.13) to (7.14) respectively, and obtained the following equations

\[ -P_{CF} \frac{\partial^2 C_{CF}}{\partial x^2} + \int_0^x (C_{CF}' - C_{CF}') \, dx - D_{CF} h_1 \frac{2C_{CF}}{x^2} = N + P_{CF}^* (C_{CF}' - C_{CF}) \]

\[ 0 \leq x \leq L_1 \] (7.40)

\[ A \frac{\partial^2 C_{CF}}{\partial x^2} - D_{CF} h_2 \frac{2C_{CF}}{x^2} = 0 \]

\[ L_1 \leq x \leq L_1 + L_2 \] (7.41)

These equations are non-dimensionalized using non-dimensional variables from equation (7.20). We have
\[
\delta_1 \frac{\partial \bar{C}_{CF}}{\partial x} + \int \bar{C}_{CF} \, dx - \frac{\partial^2 \bar{C}_{CF}}{\partial x^2} = n + \delta_2 \bar{C}_{CF} \quad (7.42)
\]
\[
\frac{\partial \bar{C}_{CF}}{\partial x} - \delta_3 \frac{\partial^2 \bar{C}_{CF}}{\partial x^2} = 0 \quad (7.43)
\]

in which
\[
\delta_1 = \frac{L_i u_0}{D_{CF} h_1} \quad (7.44)
\]
\[
\delta_2 = \frac{p L_i^2}{D_{CF} h_1} \quad (7.45)
\]
\[
\delta_3 = \frac{D_{CF} h_2}{L_2 u_0 A} \quad (7.46)
\]

In order to solve equations (7.42) - (7.43) by numerical method, we employ the finite difference functional iterative scheme as discussed by Crochet et al (1984).

We make use of constant intervals \( \Delta x \) in the \( x \)-direction and consider a grid point \( x_i = i \Delta x \) in relation to the origin \( 0 \) in equation (7.42) and \( x_j = 1 + i \Delta x \) in relation to the origin \( 1 \) in equation (7.43). The value of the function \( C(x) \) at this point is denoted by \( C_i \) and \( C_j \) respectively.

The implicit functional iterative scheme for the differential equations (7.42) - (7.43) is
\[
\begin{bmatrix}
[K+1]
\end{bmatrix}
\begin{bmatrix}
\delta_i C_{i+1} \\
\delta_i C_i \end{bmatrix}
+ \begin{bmatrix}
[K+1]
\end{bmatrix}
\begin{bmatrix}
\delta_i C_{i-1} \\
\delta_i C_i \end{bmatrix}
= n \quad (7.47)
\]

in which
\[ a_i = - \frac{\delta}{2 \Delta x} A_i C_i^m - \frac{1}{(\Delta x)^2} \]

\[ b_i = \left[ \frac{2}{(\Delta x)^2} - \delta_2 \right] \]

\[ d_i = \frac{\delta}{2 \Delta x} A_i C_i^m - \frac{1}{(\Delta x)^2} \]  

(7.48)

The contravariant suffices, \( K \) in square bracket denotes the iteration number.

\[ e_j + C_{j+1} + f_j C_{j-1} + g_j C_j = 0 \]  

(7.49)

in which

\[ e_j = \left( \frac{1}{2} - \frac{\delta_3}{\Delta x} \right) \]

\[ f_j = - \left[ \frac{1}{2} + \frac{\delta_3}{\Delta x} \right] \]  

(7.50)

\[ g_j = \frac{\delta_3}{\Delta x} \]

The discrete representation of \( \int_0^x (C_{CF} - C'_{CF}) \, dx \)

is approximated by

\[ \frac{1}{2} C_0 + C_1 + \ldots + \frac{1}{2} C_M \]  

(7.51)

as suggested by Andrietti in 1986 and \( M \) is the number of grid point.

We choose a linear approximation as the initial iterate of equation (7.40) of the form
\[ C_{GF}^0 = \frac{\Delta C_{GF} P_w L}{u_0} i \Delta x \]  

(7.52)

In order to obtain the approximate solution of equation (7.40) at particular value of constants, successive approximations are obtained. At each iteration step, the tridgional system with B.C.'s and matching conditions is solved by Newton-Raphson iterative method. The results obtained by this method has been compared with those obtained above by the approximate method.

The present chapter is concerned with the production of cerebrospinal fluid by the choroid plexuses. Therefore, for the computational purposes we introduce the parametric values for brain. The results of the analysis are discussed through the graphs in Figure (7.2) to (7.9) in the following sections.

7.4 RESULTS AND DISCUSSION

In Figure (7.2), the dimensionless concentration profiles in the extracellular channel have been depicted. The effects of concentration difference and active solute strength on the concentration have been shown. We observe from this figure that the concentration decreases monotonically towards the tight junction. As the value of \( \Delta \bar{C} = \frac{\Delta C P_w L}{u_0} \) increases, the concentration in the extracellular channel considerably increases. An increase in active solute pump strength causes increased transport of solute out of the
Fig. 7.2 Non-dimensional concentration profiles in the extracellular channel of the choroid epithelium for $K_1=2, h=0.04, l=8 \times 10^{-3}$
channel into the cell interior decreasing the concentration in the channel. Similar conclusions are drawn from this figure. The most important feature of the graph is that the concentration distribution in the channel is independent of pressure across the end stations of the channel. Therefore, when $\Delta C = 0$ the concentration in the channel is dependent upon only active pump solute strength.

A graph width-ratio, $h_1$ versus exit solute concentration ($C(x = 1)$) have been plotted in Figure (7.3). This graph represents the geometrical effect of tight junction on the solute concentration at channel exit that tends to reach the ventricular space, in other words, the effect of tight junction on the solute reaching the ventricular space through the tight junction has been depicted in this graph. The concentration goes on increasing in the beginning to attain its maximum value for certain range of geometrical ratio $h (= h_2/h_1)$ i.e. $0 \leq h \leq 0.8$. Thereafter (i.e. $0.8 \leq r \leq 0.28$) it becomes almost constant. Also, we have studied the effect of group parameter $k_1$. An increase in $k_1$ causes larger leakage of solute in cell anterior reaching the concentration in the channel. This, in turn, decreases the concentration at $x = 1$. Similar results are obtained from this figure.

In Figure 7.4, the volume flux profiles for different values of $\Delta P$ and $n$ and particular values of other parameters have been depicted. Evidently, volume flux is increasing
Fig. 7.3 Effect of variation of non-dimensional width on the exit solute concentration $x=1$
Fig. 7.4 Effect of pressure difference $\Delta P$, and active solute strength, $n$, on the volume flux profiles in the extracellular channel of the choroid epithelium $\Delta C = 0$. 
with $\Delta P$ while an increase in $n$ decreases the volume flux. As the pump strength $n$ increases, there is more passive transport of water into the cell interior reducing the volume flux in the extracellular channel. Also volume flux decreases as $k_1$ increases.

In Figure 7.5, we have described fractional concentration distribution due to active pump located at the lateral surfaces of the cleft for different values of parameters $k_1$ and $\bar{A}$. The total concentration distribution in the extracellular channel is equal to the sum of osmotically driven concentration and concentration driven by local osmosis. An increase in $n$ causes decrease in concentration, $C_n$, driven by only active pump and also in total concentration but decrease in total concentration is comparatively small. Therefore, fractional concentration due to active pump decreases. It is clear from the graph that solute concentration transported by active pump is about 60-70% at $K_1 = 2-4$.

We have plotted the solute concentration distribution due to the only concentration difference in the extracellular channel for different values of $K_1$ and $\Delta \bar{C}$ in Figure 7.6. The concentration in the channel increases as $\Delta \bar{C}$ increases. We know that osmotically driven concentration, $C_c$, increases as $\Delta \bar{C}$ increases and total concentration also increases with increase in $\Delta \bar{C}$ but increase in $\Delta \bar{C}$ is less as compared to that in $\bar{C}_c$. Therefore the ratio $C_c/\bar{C}$ increases.
Fig. 7.5 Effect of $\bar{n}$ and $K_1$ on the fractional concentration distribution driven by the active-pump.
Fig. 7.6 Effect of $\Delta C$ and $K_1$ on the fractional concentration distribution driven by concentration difference in the extracellular channel of the choroid epithelium.
A graph of exit volume flux versus width ratio has been plotted in Figure 7.7. From this graph, we have studied the influence of width-ratio on the volume flux at the channel exit i.e. reaching the ventricular space directly through the tight junction. We observe from the graph that the flux increases in the beginning with increase in the ratio and attains its peak value. After that the variation i.e. increase in the flux becomes almost zero in response to change in the width-ratio, volume flux increases upto 2.4 and for the values over that limit. The volume flux remains constant. An increase in $K_1$ or $\Delta P$ increases the volume flux. When the pressure differential across the channel increases, more volume flux is driven, through the tight junction in order to reach the ventricles.

The results for concentration distribution of the solute in the intracellular space obtained from finite-difference method are presented by plotting dotted curve in Figure (7.9). Evidently dotted curve does not show a definite and regular trend, i.e. a zig-zag nature of the distribution is observed. On the contrary, the solid curve which indicate concentration distribution of the solute obtained from approximate analytical solution exhibits a smooth and regular trend. Thus, due to non-availability of experimental results the two methods discussed in this chapter can not be compared nicely. However, one may
Fig 7.7 Effect of variation of non-dimensional width on the exit volume flux
Fig. 7.8 Comparison of solute concentration profiles obtained by analytical and finite difference methods for $k_1=2$, $h=0.04$, $l=8 \times 10^{-3}$, $\bar{n}=0.4$, $\Delta \bar{z}=1$. 

$\bar{x}$

$\bar{C}$

$0$ $0.2$ $0.4$ $0.6$ $0.8$ $1.0$

$0$ $0.2$ $0.4$ $0.6$ $0.8$ $1.0$ $1.2$
observe from the Fig. (7.9) that the curve obtained by Segal's approximation is smooth whereas the discrete point obtained by finite difference method is not continuous. We may conclude from this Segal's isotonic convection approximation is better.

The observed discrepancy can be attributed to the discretization error, etc.