University of Cape Coast

Modeling and Analysis of Ion Permeation in ACh Membrane Channels

By

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in partial fulfillment of the requirements for the award of Doctor of Philosophy Degree in Mathematics

JUNE, 2004

CANDIDATE'S DECLARATION

I hereby declare that this thesis is the result of my own original research and that no part of it has been presented for another degree in this University or elsewhere.

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We hereby declare that the preparation and presentation of the thesis were supervised in accordance with the guidelines on supervision of thesis laid down by the University of Cape Coast.

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ABSTRACT

This study is concerned with a transport process in the membrane ion channel, which is complicated by the presence of protein walls. The walls of actual biological channels have complicated shape geometries. These geometries pose a serious problem for calculation of electrical forces acting on an ion in the channel. Since proteins forming the channels have a low dielectric constant (2) compared to the water (80) in which ions move, the channel boundary plays a significant role in determining the electric forces. This interaction between ions and electric forces determines many of the properties of ion channel. In this respect, analytical solutions satisfying the Dirichlet boundary conditions for cylindrical and toroidal boundaries are presented. It appears that for realistic studies of ion transport in biological channels these geometries can describe the channel more accurately and the model system offers us the ability to reduce complex biological systems to the form that can be treated theoretically.

Table of Contents

Pages

LIST OF FIGURES

Introduction

Understanding the function of any biological systems means understanding how a biological system uses physical laws to perform the function. Most of the biological systems have complex structures and, in most of the cases, it can be difficult to recognize the physical laws associated with them. This work is an attempt to look at membrane channels and their geometries, which are crucial component in shaping the electrical properties of the nervous system.

It focuses on a prototype channel geometry for acetylcholine receptor channel. We study simplified realistic model geometry for Ach receptor channels in which analytical tractable solutions to the Poisson's and Laplace's equations can be obtained. This will allow us to examine the conductance of ions and associated membrane potentials.

In chapter one, we present the biological background to the thesis. Then in chapter two, we discuss the physics of biological channel and electrostatic potential of ACh channels in particular. In chapter three, we present justification for our approach. In chapter four, we introduce our mathematical model. Chapter five is devoted to biological implications and outlook

CHAPTER ONE

BIOLOGICAL BACKGROUND

1.1 Introduction

Membranes perform many functions. They physically and chemically isolate cells from their environments. Membranes control the passage of solutes and water between the inside and outside of the enclosed cells. To do that, membranes house a variety of channels, carries, and pumps whose transport properties are controlled by several classes of physicochemical variables and are modulated by signaling molecules such as hormones. Membranes also house signaling molecules by which intracellular sites can receive signals present in extracellular environment without the signal-carrying molecules entering the cell.

Living organisms - from simple, single-cell organisms such as bacteria to complex, multicell organisms such as humans - exchange matter with their external environment. Organisms take up nutrients and excrete waste products. Single-cell organisms extract nutrients directly from their external environments. However most cells of complex organisms are not in direct contact with external environment, but rather are in contact with the internal environment. The internal environment consists of interstitial fluids that

communicate with blood and lymph. Complex systems have elaborate organ systems that are in contact with both the external and internal environments (respiratory system, digestive system, circulatory system). For instance, the purpose of the digestive system is to break down the food into building block molecules - such as amino acids, monosaccharides, fatty acids, etc. - that are usable by cells. It is difficult to underestimate the importance of membrane transport mechanisms.

1.2 Cell Membrane Structure

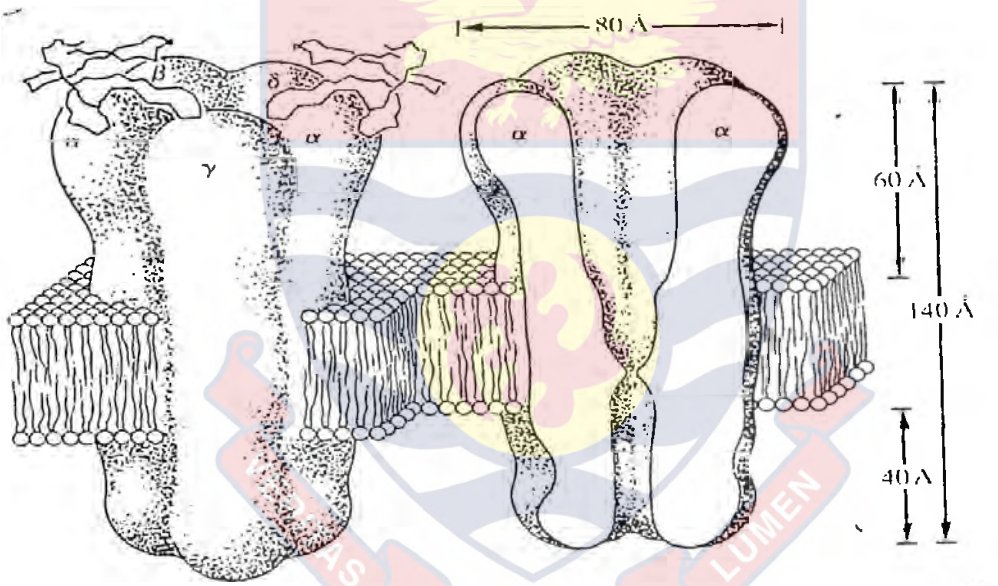

Fig.1.1 Structure of the nicotinic ACh receptor.

The structure is from image reconstruction analysis, employing electron microscopy.(Siegel G.,et al.,1991)

Membranes are composed of lipid bilayers and partially or fully integrated proteins. Lipid bilayers are freely permeable to water and small nonpolar molecules, such as oxygen (O) and nitrogen (N), but impermeable to ions. Ions can pass through the membrane only via special proteins molecules embedded in it. Ion channels form one group of those proteins; they permit rapid flow of ions across the membrane. Ion channel contains a central pore that can be opened by conformational change to allow ions to flow from one side of the membrane to the other. This arrangement allows ions to flow through channels at rates up to 100 million ions per second when it is open.

Ion channels vary considerably in their gating, by which we mean the factors that make them open or close. Some channels are opened by combination with particular chemicals outside or inside the cell, such as neurotransmitters or cytoplasmic messenger molecules. Others are opened by changes in the voltage across the membrane, and yet others by sensory stimuli of various kinds.

Channels show selectivity in the ions that permeate. Some of them permit only particular ions, such as sodium, potassium, calcium or chloride

ions. Others are selective for a broader group of ions such as monovalent cations, or cations in general.

These two aspects of channel functioning, i.e gating and selectivity, are conceptually distinct from one another. Molecular structure studies confirm this view: parts of the channel molecule concerned with gating seem to be separate from those concerned with selectivity. Transmitter-gated channels are quite different from voltage-gated channels and their relatives. They show little or no sequence similarity and have distinct structures.

The first channel to be studied in detail was the nicotinic ACh receptor ('nAChR', or simply"AChR'). Nicotinic ACh receptors are expressed in postsynaptic membranes of skeletal muscle fibers, in neurons throughout the nervous system.The receptors are activated by ACh released from presynaptic nerve terminals, and on activation they too form channels through which cations can enter or leave the postsynaptic cell. They are designated 'nicotinic' to reflect the fact that the actions of ACh are mimicked by nicotine, and to distinguish them from the very different ACh receptors (mAChRs), that can be activated by muscarine. Muscarine receptors are not ion channels; instead their activation sets in motion intracellular messenger systems that, in turn, affect ion channel activity.

The size and the orientation of intact channel with respect to the lipid membrane is determined by the high-resolution microscope imaging, and other physical techniques. The molecule is about 8.5 nm across at its widest point, which is in the extracellular domain, and about 11 nm long. The extracellular portion extends about 5 nm above the surface of the membrane. The central pore is about 0.7 nm in diameter.

1.3 Electrostatic Potential in the ACh Channel

In general, the interior of a cell has a lower potential than the exterior. The lower potential makes it electrically negative to the exterior. This potential difference, which ranges between –20 and –200 mV for different cell types is termed the resting potential, Changes in the resting potential elicit important changes in the excitability of cells.

Within the channel, the potential is determined not only by the resting potential of the cell, but also by the interaction between ions passing through the channel, The electric potential profile determines many key properties of the channel such as gating and ion selectivity (Kuyucak et.al, 1998). In the ACh channel, for example, selectivity is mainly determined by the presence of fixed charges in the constricted section of the channel. Typically, ion channels have excess charges on the proteins walls that contribute to the determination

of their selectivity properties. In the ACh channel, fixed charges are located in the protein wall (Kuyucak et al, 1998). Structural studies suggest that they are located near the constricted sections of the channel (Unwin, 1989). The fixed charges contribute to the presence of an energy barrier in the narrow, constricted section of the channel and play a key role in the ion-selectivity property. Apart from interacting forces made up of induced charges, ion-ion interaction, ion-solvent interaction and Van der Waals forces, there is also a random activation of the groups of synapses, which in turn elicit action potentials. An action potential is initiated, for example, when a synaps or a group of synapses is activated due to chemical influx. When ions permeate the ACh channel, the potential difference across the membrane could be increased or decreased, depending on the polarity of the ions. In the ACh channel, sodium and potassium are the main chemicals that cause changes in potential. The influx of sodium ions leads to a decrease in the potential difference that triggers depolarization. The channel potential is thus generated by the differences in the ionic makeup of the intracellular and extracellular fluids.

With this brief biological background, we shall consider the physics of biological channels in the next chapter.

CHAPTER TWO

THE PHYSICS OF BIOLOGICAL CHANNELS

2.1 Introduction

Molecular biophysicists strongly believe that the function of ion channels is a consequence of a molecular structure. It should be possible to predict the electrophysiology of an ion channel precisely if one knows the structure and its relationship to the surrounding membrane and electrolyte. However, even such a small biological system as a single ion channel is a complicated structure with many degrees of motional freedom. The smallest known ion channel, gramicidin, contains just 30 amino acids, and has a precisely known structure. To do a molecular dynamics simulations of ion permeation for a gramicidin channel, i.e. to see enough ions go through the channel to get a direct measure of the current voltage (I-V) curve, one would need to simulate about one-tenth of a microsecond, or about 100,000h of CPU time (Jacobsson E.,1998). This is obviously an impractically large amount of time with present technology and with technology available in the foreseeable future. To overcome this obstacle to direct simulations, it is necessary to use statistical mechanics combined with simulations to structure the problems into

hierarchies of descriptions at different levels of detail. Probably following this idea, in the last 10-15 years the field of ion channels has entered the rapid phase of development. Despite this development, some of the outstanding questions about how biological channels work remain unanswered. The first question details dynamical processes underlying the permeating of ions across an open channel. Secondly, all biological ion channels are selectively permeable to a specific ion. This selectivity mechanism needs to be understood in terms of the interactions of the permeating ions with the surrounding water and protein molecules. Thirdly, what determines the upper-limit in channel conduction? To be functionally effective, a channel must process a large number of ions, but at the same time, it has to be highly selective to specific ionic species. What kind of structural changes take place when the channel makes transitions from the close conformation to the open conformation? Finally, the tertiary structure of all known ionic channels needs to be determined. The advance in the studies of ion channels has been brought about by the combined efforts of experimental and computational biophysicists. As new analytical methods have been developed and the available computational power increased, theoretical models of ion permeation have become increasingly sophisticated. Now it has become possible to relate the atomic structure of an ion channel to its function, through the fundamental laws of

physics operating in electrolyte solution.

2.2 Kinetic and Thermodynamic Approach to Membrane Transport Properties

The living cell requires for its proper functioning materials that originate outside the cell; and as a result of its functioning produces materials that leave the cell. The passage of molecules across the cell membrane is known in many cases to be a purely diffusive process. There are examples of so-called active transport, which involves the use of energy obtained from chemical processes to drive molecules across membranes So, a molecule as biological system never rests; it is never in equilibrium. Equilibrium for any biological system means death. Since diffusion is an example of the approach to equilibrium, a system in which diffusion is observed cannot be at equilibrium. It follows that the use of classical thermodynamics is theoretically suspect. Non-equilibrium thermodynamics is the theory that addresses itself specifically to the relationship between flows and thermodynamic parameters and often provides conditions under which other theories must comply.

According to non-equilibrium thermodynamics, the force acting on a single ion i in a continuous system is the negative gradient of its electrochemical potential i.e, $-\nabla\mu_i$ where μ_i is the i-th electrochemical potential.

However, if the particles have an electric charge and if they are subjected to an electric potential gradient, transport will arise from two physical mechanisms: diffusion due to a particle concentration gradient and drift (also called migration) due to an electric potential gradient. The Nernst-Planck equation (sec.2.3) expresses the current density of the species of the charged particles in terms of the concentration and potential gradient. If the species of the charged particles is conserved, then the current density and concentration of the particle are also linked to a continuity equation. Finally, the concentrations of all the charged particles in electrodiffusion are linked to the electric potential via Poisson's equation. We describe below Nernst-Planck equation and related equations used in modeling the flow of ions through channels.

2.3 The Nernst-Planck Equation

The particles in the medium are scattered because their thermal kinetic energy causes collisions with particles of the medium. The collision process causes no net velocity of each particle, but does cause the net flux ϕ of particles down their concentration gradient .From Fick's first law of diffusion, we have

$$\phi_{diffusion} = -D\frac{\partial c}{\partial x}, \tag{2.1}$$

where $D = l^2/2\tau$, with l and τ as the mean free path and the mean free time, respectively. Suppose that particles also experience a body force in a positive x-direction, implying that between collisions the particles will be accelerated in the x-direction. The acceleration causes an increase in velocity in the x-direction during the interval between collisions. This drift velocity is $V = uf$, where f is the force of a mole of particles and u is the molar mechanical mobility. The flux of particles due to their drift is

$$\phi_{drift} = cV = cuf \tag{2.2}$$

Suppose the particles are charged with valence z and the body force is caused by an electric field with electric field intensity $\varepsilon = -\partial \psi / \partial x$, where ψ is an electric potential. Then the force expected on a mole of particles is $f = zF\partial\psi/\partial x$, where F is a Faraday's constant (the charge on a mole of univalent particles), which is about $9.65\ 10^4$ C/mol. In this case, we can rewrite equation (2.2) as

$$\phi_{drift} = -cuzF\frac{\partial \psi}{\partial x} \tag{2.3}$$

The kinetic model of the motion of a particle suggests that the instantaneous velocity of each particle is the sum of the drift and diffusion velocities. Therefore , it is reasonable to conclude that the net flux of particles is the sum of that caused by drift and diffusion.

For any ion species n, the flux due to diffusion and the drift is

$$\phi_n = \underbrace{-D_n \frac{\partial c_n(x_1 t)}{\partial x}}_{\text{Diffusion}} \underbrace{- u_n z_n F c_n(x_1 t) \frac{\partial \psi(x_1 t)}{\partial x}}_{\text{drift}} \tag{2.4}$$

where D_n is the diffusion coefficient, C_n is the concentration of ions, u_n is the mobility, and z_n is the valence of the *n-th* ion. The dimensions are as follows, $\partial\psi(x_1 t)\partial x$ is the potential gradient in $N/C; z_n F$ is the charge of a mole of ion n in C/mol; $z_n F(\partial\psi\ (x_n t)/\partial x)$ is the force on a mole of particles in N/mol; $u_n z_n F(\partial\psi\ (x_n t)/\partial x)$ is the velocity of the particles in m/s; and the flux is the product of the velocity and the concentration (T. F. Weiss, 1996).

The current density $J_n(x,t)$ in A/cm^2 is related to the flux by

$$J_n(x,t) = -z_n F \phi_n(x,t) \tag{2.5}$$

Substituting eqs. (2.1) and (2.3) into eqn (2.5) yields

$$J_n(x,t) = -z_n F\left(D_n \frac{\partial c_n(x,t)}{\partial x} + u_n z_n F c_u(x,t) \frac{\partial \psi(x,t)}{\partial x} \right) \tag{2.6}$$

This equation is known as the Nernst-Planck equation of electrodiffusion The Nernst-Planck equation can be expressed in several useful and equivalent forms. Using the Einstein relation , $D_n = u_n RT$, for example the Nernst-Planck equation can be expressed as

$$J_n(x,t) = -u_n z_n F c_n(x,t)\left(\frac{RT}{c_n(x,t)} \frac{\partial c_n(x_n t)}{\partial x} + z_n F \frac{\partial \psi(x_n t)}{\partial x} \right) \tag{2.7}$$

which can be rearranged to yield an expression in terms of the logarithmic derivative of concentration

$$J_n(x,t) = -u_n z_n F c_n(x,t) \frac{\partial}{\partial x}(RT \ln c_n(x,t) + z_n F \psi(x,t)) \tag{2.8}$$

2.4 The Electrochemical Potential

The Nernst-Planck equation can also be expressed as

$$J_n(x,t) == -u_n z_n F c_n(x,t) + \frac{\partial \tilde{\mu}(x,t)}{\partial x} \tag{2.9}$$

where

$$\overline{\mu}_n(x,t) = \mu_n^0 + RT \ln c_n(x_1 t) + z_n F \psi(x,t) \qquad (2.10)$$

Here μ is the electrochemical potential, and μ_n^0 is its reference value at unit concentration and zero potential. Note that the two terms that depend on solute concentration and potential are the stored chemical energy and the stored electrostatic energy per mole, respectively.

Thus, the flux of ions and the current density carried by the ions are proportional to the electrochemical potential gradient.

2.5 Conservation of Particles and Charge

If each ionic species is conserved, each ion will satisfy its own continuity equation

$$\frac{\partial J_n(x_1 t)}{\partial x} = -zF \frac{\partial c_n(x_1 t)}{\partial t} \qquad (2.11)$$

If each of the particles is conserved, the charge on population of charge particles will also be conserved. This result can be seen by summing the eq (2.11) over all the charge species.

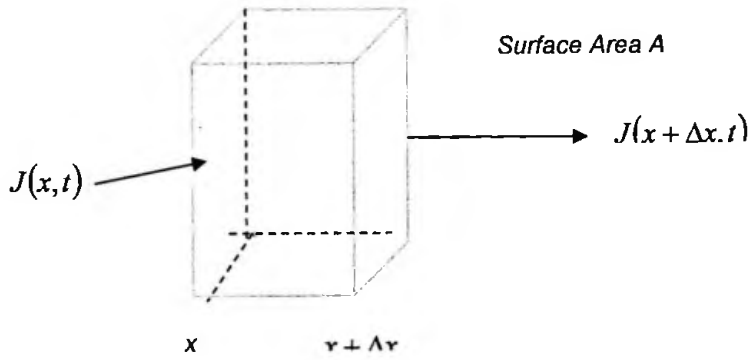

Figure 2.1. Volume element used to derive concentration of change.

Consider the incremental volume element of cross-sectional area A and width Δx with charge density and current density. Conservation of charge implies that the net charge flowing into the volume element in a time interval of duration Δt must equal the increase in charge in the volume element. Therefore,

$$J(x,t)A\Delta t - J(x+\Delta x,t)A\Delta t = \rho(x,t+\Delta t)A\Delta x - \rho(x,t)A\Delta x \tag{2.12}$$

Rearranging the terms in the equation (2.12) and letting $\Delta x \to 0$ and $\Delta t \to 0$ yields

$$\frac{\partial J(x,t)}{\partial x} = -\frac{\partial \rho(x,t)}{\partial t} \tag{2.13}$$

this in three dimension can be written as

this in three dimension can be written as

$$\nabla . J = \frac{\partial \rho}{\partial t} \tag{2.14}$$

2.6 Poisson's Equation

Poisson's equation, which is derivable from Gauss's law, links the charge to electric potential as follows:

$$\frac{\partial^2 \psi(x,t)}{\partial x^2} = -\frac{\rho(x,t)}{\varepsilon}, \tag{2.15}$$

where ρ is the charge density (C/cm), ψ is the electric potential, and ε is the permittivity of the medium. The charge density consists of the two terms: the mobile ionic charges or the fixed (immobile) charges in the medium. Thus,

$$\rho(x,t) = F\sum_{n=1}^{N} z_n c_n(x,t) + \rho_f(x,t) \tag{2.16}$$

where ρ_f is the fixed charge density.

An electrodiffusion system is completely specified by eqs (2.7),(2.11),(2.15) and (2.16). There are N Nernst-Planck equations linking

the 2N+1 variables $J_1, J_2, \ldots J_u, c_1 c_2 \ldots c_u, \psi$,. If the ions are each conserved, then there will be an additional N continuity equations that link these variables. The final relation linking the 2N+*1* variables is Poisson's equation (2.15). If the fixed charges are specified as a material property, and if appropriate boundary conditions are specified, then these equations constitute the complete specification of electrodiffusion problem; that is, there are 2N+1 variables and equations. These equations can be solved for the concentration and current density of each of the mobile ions as well as the electric potential. However, these equations can be nonlinear because of the term $c_n(x,t)\partial\psi(x,t)/(\partial x)$ in eq.(2.7), which complicates their solution. (T. F. Weiss, 1996).

2.7 Electrodiffusive Equilibrium Condition

From the Nernst-Planck equation we can directly determine the conditions that must apply at electrodiffusive equilibrium, i.e. the conditions at which the flux of the *n-th* ion is zero. If we set $J_n = 0$ in eq.(2.8) and if we recognize that at electrodiffusive equilibrium all the variables are time independent, then we obtain the conditions

$$-u_n z_n^2 F^2 (x,\infty)\frac{d}{dx}\left(\frac{RT}{z_n F}\ln c_u(x,\infty)+\psi(x,\infty)\right)=0 \qquad (2.17)$$

There are several ways to satisfy the ellectrodiffusive equilibrium conditions. Three of these are trivial:

(i) if $u_n = 0$, which occurs if the particles are fixed and cannot drift or diffuse.

(ii) if $z_n = 0$, which implies that the particles are uncharged and do not carry a current even if they can diffuse.

(iii) if $c_n = 0$, which occurs if there are no particles. A more interesting case occurs if $u_n \neq 0$, $z_n \neq 0$, and $c_n \neq 0$. Then we can divide these terms out of eq. (2.17) so that this condition is

$$\frac{d(\ln c_n(x,\infty))}{dx} = -z_n\beta\frac{d\psi(x,\infty)}{dx}, \qquad (2.18)$$

where $\beta = F/RT$.

This condition can be integrated to yield

$$c_n(x,\infty) = c_n(x_0)e^{-z_n\beta(\psi(x,\infty)-\psi(x))} \qquad (2.19)$$

where location x_o provides a point of reference for a potential. The equation gives the spartial distribution of charged particles in an electrostatic field at electrodiffusive equilibrium.

2. 8 Electroneutrality.Charge Relaxation Time

The strong forces of attraction between oppositely charged ions in a solution tend to neutralize the net charge in the solution. There is a strong tendency for this charge neutralization to occur, and the resultant property of the solution is called electroneutrality. How long will it take for electroneutrality to be established? The charge relaxation time is the measure of the time scale for establishing electroneutrality.

In an electrolytic solution with uniform composition the current density is related to the electric field (negative gradient of the electric potential) according to Ohm's law

$$J = \sigma_e \varepsilon \ , \quad \text{where } \varepsilon = -\nabla \psi$$

where σ_e is the electric conductivity of the medium.In a homogenious conductor

$$\nabla \cdot J = \sigma_e \nabla . \varepsilon$$

But Gauss's law implies that $\nabla \cdot (c\varepsilon) = \rho(t)$, where $\rho(t)$ is the charge density (C/cm^3) at time t. Therefore,

$$\nabla \cdot J = \sigma_e \nabla \cdot \varepsilon = \frac{\sigma_e}{\varepsilon} \rho \tag{2.20}$$

If we substitute the equation for the continuity of charge eq. (2.13) into eq. (2.20) under the assumption that the charge density is increased uniformly in the solution, we obtain

$$\frac{d\rho(t)}{dt} + \frac{\sigma_e}{\varepsilon} \rho(t) = 0,$$

which has the solution $\rho(t) = \rho(0) e^{-t/\tau_r}$ where τ_r is the charge relaxation time given by

$$\tau_r = \frac{\varepsilon}{\sigma_e}.$$

Thus, for spatially uniform distribution of charge (so that no diffusion takes place) the charge density relaxes exponentially to zero and the charges move to the boundaries of the solution, i.e. they get as far away from each other as possible. The time constant for this relaxation can be computed for the physiological saline solutions which is

0.7 nanoseconds.

2.9 The Debye Length

I n determining the debye length , we need to solve the Poisson equation which is given as

$$\frac{d^2\psi}{dx^2} = -\frac{\rho}{\varepsilon} \tag{2.21}$$

where ρ is the charge density and ε is the permittivity. For each ion the equilibrium condition is

$$c_+(x) = Ce^{-zF\psi(x)/RT} \quad \text{and} \quad c_-(x) = Ce^{zF\psi(x)/RT} \tag{2.22}$$

where we have assumed that $\psi(\infty) = 0$, which is used as a reference for the potential.(see eqs(2.18)and(2.19)). Eqs (2.21) and (2.22) are linked by the equation

$$\rho(x) = z_+Fc_+(x) + z_-Fc_-(x) \tag{2.23}$$

Now, substituting eq .(2.22) into (2.23) and the result into eq. (2.21), we obtain the Poisson-Boltzman equation

$$\frac{d^2\psi(x)}{dx^2} = -\frac{1}{\varepsilon}\left(z_+FCe^{-zF\psi(x)/RT} + z_-Fce^{zF\psi(x)/RT}\right) = \frac{2zFC}{\varepsilon}\sinh\left(\frac{zF\psi(x)}{RT}\right) \tag{2.24}$$

The Poisson-Boltzman equation can also be expressed in normalized coordinates as

$$\frac{d^2\psi(x)}{\partial X^2} = \sinh\psi(x) \tag{2.25}$$

where

$$\psi(x) = \frac{\psi(x)}{RT/zF}$$

is the normal potential.

$$X = \frac{x}{\Lambda_D}$$

is the normalized distance, and Λ_D is called the Debye length and is expressed as

$$\Lambda_D = \sqrt{\frac{\varepsilon RT}{2z^2F^2C}}$$

Therefore, the Debye length is a measure of the spatial extent of the potential distribution and a measure of a distance over which the electroneutrality is violated.

The Nernst-Planck equation is the starting point for many significant

calculations in aquous solutions, in ion channels, and in semiconductor devices. It is always necessary to integrate the differential equation for the given boundary conditions, for example from the internal aquous solution to the external. This is difficult because one must know the concentration (activites) of all ions, their diffusion coefficients, and the electric field at every point on the way. Since for most problems these quantities are not known, many model solutions make highly simplifying assumptions.

We mention three prominent simplified approaches (reviewed by Sten-Knudsen, 1978)

1.To make calculations easier in free diffusion systems, (Nernst, 1888) and (Planck, 1890) assumed that at all points, the anion and cation charges cancel out exactly so the system is everywhere eletroneutral, (the electroneutrality condition).

2. To calculate diffusion potentials in liquid junctions, (Henderson ,1907) supposed that the two aqueous solutions mix linearly as one proceeds through the junction.

3. For biological membranes, and today for channels, (Goldman ,1943), (Hodgkin and Katz ,1949) introduced three assumptions: (a) The electric potential drops linearly across the membrane (constant field); (b) each ion is

uninfluenced by any other ions (no interactions and no elctroneutrality considerations); and the diffusion coefficients and activity coefficients do not vary along the channel.

The more rigorous approach to solving the Nernst-Planck equations calculates the electric field from first priniciples (Eisenberg ,1996) without presupposing its shape. The electric field is always central as it is the major force on the ions and it profoundly affects their distribution and motion. The calculation uses Poisson's law, a fundamental rule of electrostatics that all potential differences arise because of the tiny deviations from electroneutrality in each small volume. In one dimension, Poisson's law states the local second spatial derivative of the potential,

$d^2\psi/dx^2$, is given by $-\rho/\varepsilon\varepsilon_0$, where ρ is the local concentration of excess charge and ε is the dielectric constant of the medium. For electrodiffusion in macroscopic media, the Nernst-Planck equations and Poission's equation are solved simultaneously, yielding the internal electric field and concentration profiles. The Possion-Nernst-Planck (PNP) model has been thoroughly studied by (Levitt ,1991a; Chen and Eisenberg ,1993; Eisenberg ,1996; Nonner and Eisenberg ,1998). Such PNP models also ready accommodate local immobile charges and can include partition coefficients and activity coefficients

(collectively called "excess free energies"). PNP models give the most fundamental solutions of the Nernst –Planck equations in macroscopic diffusion regimes.

All the Nernst-Planck-derived models are continuum models. They do not identify or follow individual particles. They use average concentrations and assume that ions move in average electric field. If they calculate the electric field, they do so as average electric fields,which is nothing more than the mean field approximation. The various simplifications used in each model lead to insightful partial descriptions of potentials and fluxes. Some of the assumptions are more acceptable for macroscopic media than for those of atomic dimensions, like ion channels. Although, the results are models that ignore certain physical facts in order to obtain tractable expressions, all are useful and advance our understanding.

In the next section , we shall describe the dynamics of nonequilibrium systems which are better described under stochastic dynamics.

2.10 Stochastic dynamics

There are several tools in statistical mechanics that treat the dynamics of nonequilibrium systems, the most widely known is a theory of Brownian motion. The behavior of an ion in the electrolyte solution undergoing the random type of motion can be described by the dynamical equation of motion in classical mechanics, known as the Langevin equation.

In common with Nernst-Planck models, Brownian Dynamics models (Cooper et.al. 1985;Chang et al. 1998) represent the solvent as a continuum having a frictional coefficient for each ion species and a dielectric constant. However, in Brownian dynamics the individual trajectories of each ion are calculated in time, so one gets a movie of the motions of every ionic particle. Every ion follows a path as it is driven by 1) a random force that models molecular collisions and by 2) electric forces that come from external fields, local fixed charges, and all the other local jiggling ions. In one approach to Brownian dynamics (Chang et al.1998), trajectories are computed from Newton's laws of motion, which for each particle relates the product of its mass and acceleration (m a) to the sum of three kinds of forces on the particle (Langevin, 1908)

$$m_i a_i = z_i q_e \frac{d\psi}{dv} - f_i \frac{dx}{dt} + \text{(random force)}$$

Here, the first term on the right hand side is the electric force and the second is the frictional force proportional to velocity. The last term, a stochastic variable simulating the collisional forces, has a mean of zero. In calculations, the direction and magnitude of the random force are chosen at successive time points (typically 1-100 ps apart) from a random-number generator. The electric field can be calculated from the Poisson's law alone.

Because Brownian dynamics follows the fate of every particle by integrating in tiny steps of time, the calculations take much longer than those of Nernst-Planck models. For problems of electrodiffusion in large spaces, Brownian dynamics and Poisson-Nernst-Planck models give equivalent, correct answers (Corry et.al.2000). However, as a diffusion space shrinks to the size of ion channels and atomic dimensions, there are advantages in dealing with discrete diffusive particles rather than using average concentrations and average electric fields and Brownian dynamics will give a physically more correct descriptions. (Cooper et.al 1985;Corry et.al. 2000) .

We, therefore, introduce the molecular dynamics solution in the next section.

2.11 Molecular Dynamic Solution

This approach is made possible by availability of channel structures that are known to atomic resolution. Until recently, the only channel that met this condition was gramicidin channel. However, with structures now available for the protein channel (Kreusch and Schulz, 1994), potassium channels (Doyle et al., 1998), iron transporting channels (Ferguson et al., 1998) and mechanosensitive channels (Chang et.al.,1998) (all from bacteria), the molecular dynamics (MD) approach now has the potential to be applied to the aforementioned biologically interesting channels. The basic idea is the following: one assembles an initial atomic model of the channel protein, the channel water, a nearby region of the channel lipid membrane, and samples of the bulk water at both ends of the channel. One then places some ions in the water, sets the temperature and applies a voltage or concentration gradient and directly measures the ion flux as a function of time as the exact atomic dynamics of the model are simulated on the computer. At each time step in the simulation, all the forces on each atom are calculated and the atom moves under this force for a time period short enough that the forces should remain constant. Unfortunately, this direct approach is still beyond our current

computational limits.

These numerical calculations also have some other limitations, beyond that of computer time. The most serious problem is a fundamental limitation in the accuracy of the atomic force constants.

To conclude this chapter, we note that there are several approaches to the study of the ACh channel. However, Laplace and Poisson equations play very fundamental role in understanding this phenomenon. We, therefore, in the next chapter look at the mathematical implications of these two equations and establish it's existence and uniqueness.

CHAPTER THREE

ON THE USE OF LAPLACE AND POISSON EQUATIONS MODELS TO DESCRIBE ION PERMEATION IN ACh CHANNELS

3.1 Introduction

The basic concepts we consider here are the link between electrostatic interactions and biological macromolecules and how they affect the flow of ions through the ACh channels. Two such concepts are "electronic charge" and "electric potential". They are related through the Laplace and Poisson equations. We herein examine the Laplace and Poisson equations through harmonic functions and establish it's properties.

Laplace and Poisson equations

The mathematical theory of potential is basically the study of Laplace equation and its related inhomogeneous Poisson equation. These are elliptic equations and therefore require Dirichlet (or Newmann) conditions on a closed boundary. Basically, Laplace equation arises in electrostatic problems, the solution being the electrostatic potential.

The equation

$$\frac{\partial^2 u}{\partial x_1^{\,2}} + \frac{\partial^2 u}{\partial x_2^{\,2}} + \frac{\partial^2 u}{\partial x_3^{\,2}} = 0 \qquad (3.1)$$

where x_1, x_2, x_3 are orthogonal Cartesian coordinates is called the Laplace equation .The equation may be written in the form $\Delta u = 0$, where

$$\Delta = \frac{\partial^2}{\partial x_1^2} + \frac{\partial^2}{\partial x_2^2} + \frac{\partial^2}{\partial x_3^2}$$

The non-homogeneous equation

$$\frac{\partial^2 u}{\partial x_1} + \frac{\partial^2 u}{\partial x_2} + \frac{\partial^2 u}{\partial x_3} = f \qquad (3.2)$$

or $\Delta u = f$,

where f is a known function is called the Poisson equation. The form of the differential expressions on the left sides of the Laplace and Poisson equations are the same in all orthogonal Cartesian coordinates. In cylindrical coordinates,(r, φ, z),

$$\Delta \equiv \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial}{\partial r}\right) + \frac{1}{r^2}\frac{\partial^2}{\partial \varphi^2} + \frac{\partial^2}{\partial z^2} \qquad (3.3)$$

and in spherical coordinates , (r, θ, φ),

$$\Delta = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial}{\partial r}\right) + \frac{1}{r^2 \sin\theta}\frac{\partial}{\partial \theta}\left(\sin\theta\frac{\partial}{\partial \theta}\right) + \frac{1}{r^2 \sin^2\theta}\frac{\partial^2}{\partial \varphi^2} \qquad (3.4)$$

(See Appendix 4 for the derivation of the Laplacian in various coordinate systems)

The mathematical problem is said to be correctly stated if a solution exists that is unique and that is a continuous function of a given set of conditions of the problem. The requirements contained in the formulation of the concept of correctness reflect our general phenomena (i) which must arise when certain necessary conditons are met (a solution exists) (ii) which are completely determined by these conditons (the solution is unique), and (iii) which are changed only slightly if the conditions are changed. The correct statement of a problem usually assures a physical meaning to the solution. The conditions assuring correctness of the statement of a boundary-value problem vary from one type to another. However there is a basic group of conditions that enter into all these formulations constituting a solution to a boundary–value problem (stated for a second-order partial differentail equation) must

(a) be continuous in the region for which the problem is posed, up to the boundary of the region,

(b) have continuous second derivatives within the region and satisfy the given equation (for example, Laplaces, Poission's),

(c) satisfy the given boundary conditions on the boundary of the region,

(d) (if the region is three-dimensional and infinite) approach zero as we displace a given point an infinite distance along an arbitrary ray contained in the region.

Solutions to boundary-value problems in three-dimensional regions satisfying these conditions will be called regular solutions.

Regular solutions to the fundamental boundary value problems are unique (sometimes under certain additional conditions) and they depend continuously on the boundary conditions. The regular solutions exist only when the given boundary conditions are sufficiently smooth. In practice, this point is not especially important, because any boundary condition within the physical meaning can be approximated to any desired degree of accuracy by smooth functions.

3.2 Harmonic functions

A function $u(x)$ is said to be harmonic at a point x if it has continuous second derivatives and satisfies the Laplace equation at that point. A function $u(x)$ is said to be harmonic in a closed region V if the following conditions are satisfied:

(i) it is continuous throughout that region

(ii) it is harmonic at all interior points of the region;

(iii) (when the region V is infinite) it approaches zero as we displace a point x infinitely far along an arbitrary ray belonging to the region.

An extreme –value theorem

If a function $u(x)$ is harmonic in a region V, it does not have maxima or minima within that region but attains its largest and smallest values on the boundary.

Proof: Let us suppose that the function u attains a maximum at a point $x \in V - F$. Consider a spherical surface σ, with center at point x, lying entirely within the region V. The radius of the sphere can be chosen sufficiently small so that

$$u(x) > u_{\max} + \varepsilon, \tag{3.5}$$

where $u_{\max}$ is a maximum value of u on σ, and ε is a positive number. Also, we can find a sufficiently small positive number η such that at an arbitrary point lying either on or within the surface ξ. Consider the inequality.

$$\eta|x-\xi|^2 < \frac{1}{2}\varepsilon, \tag{3.6}$$

where $|x-\xi|$ is a distance between the points x and ξ. Then, on the basis of inequality (3.5), the function

$$v(\xi) = u(\xi) + \eta|x-\xi|^2 \tag{3.7}$$

will exceed its greatest value on σ at the point $\xi = x$. This means that its maximum must be attained within this surface ξ. But at the point where the maximum is attained, the second derivatives with respect to the coordinates of the point ξ cannot exceed zero. However,

$$\Delta_\xi v = \frac{\partial^2 v}{\partial \xi_1^2} + \frac{\partial^2 v}{\partial \xi_2^2} + \frac{\partial^2 v}{\partial \xi_3^2} = \eta \Delta_\xi |x-\xi|^2 = 6\eta > 0 \tag{3.8}$$

The contradiction shows the impossibility of inequality (18), it follows, therefore, that the function u cannot have a maximum value within the region V.

Corollary: If two functions u and v are harmonic in a region V, satisfaction on the boundary of the region of one of the inequalities $u \le v$ or $|u| \le v$ implies the satisfaction of the same inequality within the region also.

Proof. If the function $u-v$ which is harmonic in the region, is non-positive on the boundary of the region, it must be non-positive everywhere in the region since within the region it cannot exceed its maximum value on the boundary. The assertion thus follows in the case of $u \le v$. The inequality $|u| \le v$ is equivalent to the two inequalities $u \le v$ and $-v \le u$. From what has been shown, the satisfaction of each of these on the boundary implies their satisfaction within the region as well. Hence, the assertion is also true in the case of the inequality $|u| \le v$.(Koshlyakov N. S et. al, 1964)

3.3 Removable singularity lemma

Suppose that a point $\xi = x$ is an isolated singular point of a function, $u(\xi)$ and that, at all points of some neighborhood Ω of the point x, the function $u(\xi)$ is harmonic. Then, either the function $u(\xi)$ increases no more slowly as ξ approaches x than does $1/r$

(where $r = |x-\xi|$ is the distance between the points x and ξ), or the function $u(\xi)$ has a removable singularity at the point x and can be redefined at that point in such a way that it will be harmonic there.

Proof: Let us choose a positive number a sufficiently small that the sphere consisting of points r such that $r \le a$ belongs entirely to the region Ω. It is possible to define a function that is harmonic in a sphere and that coincides on its surface with a given continuous function. We denote by $v(\xi)$ a function that is

harmonic in the sphere $r \le a$, having the same values on its surface as does the function $v(\xi)$. Let us consider the function

$$\frac{1}{r} - \frac{1}{a} \tag{3.9}$$

It is non-negative within the sphere $r \le a$ and harmonic in the region V_ϵ that is obtained by removing from the sphere $r \le a$ an arbitrarily small neighbourhood $r \le \xi$ of the point x. As ξ approaches x, the function increases in proportion to $1/r$. Therefore, if the function $u(\xi)$ increases more slowly than $1/r$ as ε approaches x (i.e., if the product ru approaches 0 as ε approaches x) then there exists a number η, which approaches 0 as ξ approaches 0 such that

$$|u - v| \le \eta\left(\frac{1}{r} - \frac{1}{a}\right) \quad \text{for } r = \varepsilon \text{ and } r = a \tag{3.10}$$

For η we can take the smallest value of the expression with $r = \varepsilon$. Since the function $u - v$ and $\eta(1/r - 1/a)$ are both harmonic in the region V_ε, then from the corollary to the extreme-value theorem, the inequality (3.10) remains valid for $\varepsilon \le r \le a$. Let us fix the point ξ by giving the left side of the inequality (19) and also the function $(1/r - 1/a)$ certain fixed values; then let the radius ϵ approach zero. The right side of the inequality (3.10) will approach zero inequality and, since its left side is independent of ε, we have $u = v$ for all $\xi \ne x$ and $r \le a$.

Thus, the function $u(\xi)$ increases more slowly than $1/r$ as ξ approaches x, then

for $\xi \neq x$, it coincides with the bounded function v and, consequently, it is bounded for $\xi \neq x$. Then, since $u - v$ for all $\xi \neq x$, we may set $u(x)$ identically equal to $v(x)$ at the point $\xi \neq x$; that is the point x is a removable singular point for the function $u(\xi)$.

Thus, a function that is harmonic at all points of a region except for a finite number of isolated points x' (where i=1,2,3,...), at which it has a non-removable singularity, increases at least as rapidly as $1/|\xi - x^i|$ as these points are approached, The function has no other kind of singular point . An example of a function with a non removable singularity at a point x^i that is harmonic at the remaining points in space is the function $1/|\xi - x^i|$.

To examine functions that are harmonic in finite regions, let us place every point x in space in correspondence with a point ξ with coordinates.

$$\xi_i = x_i \frac{a^2}{|x|^2} \left(i = 1,2,3 \; |x|^2 = {x_1}^2 + {x_2}^2 + {x_3}^3, \quad a = \text{constant} \right) \tag{3.11}$$

The transformation given by eq.(3.11) is called an inversion with respect to the spherical surface of radius a with center at the point $x = 0$. The points x and $v(\xi)$ are said to be harmonically conjugate with respect to the spherical surface referred to.

Since the relations

$$\frac{\xi_i}{x_i} = \frac{a^2}{|x|^2} \quad [\mathrm{i} = 1, 2, 3] \tag{3.12}$$

have the same values of all i, the harmonically conjugate points x and ξ lie on a single ray through the point. $|x| = 0$ Furthermore, if we calculate the distance $|\xi| = \sqrt{\left(\xi_1^2 + \xi_2^2 + \xi_3^2\right)}$ of the point ξ from the origin of the ray by use of eq (20), we see that $|\xi||x| = a^2$.

From this it follows that the geometry of the transformation in question is the same as if the space were reflected in the surface Σ of the sphere of radius a with center at the point $|x| = 0$. Points lying on Σ are mapped into themselves and points lying outside (inside) Σ are mapped into points lying inside (outside) Σ. In particular, an infinitely distant point is mapped into the $|x| = 0$ and the point $|x| = 0$ is mapped into an infinitely distant point. It is easy to show that with this inversion, curves are mapped into curves, surfaces into surfaces, and regions into regions. Infinite regions are mapped into regions containing the coordinate origin and regions containing the coordinate origin are mapped into infinite regions. Since the property of conjugacy of two points is mutual, that is since each is mapped into the other upon inversion arbitrary sets of points also have this property. In particular, if a region V is mapped into a region V' then the region V' will be mapped into the region V. The regions V and V' are said to be conjugate to each other. Suppose that V' is conjugate to the region V under inversion with

respect to the surface of a sphere of unit radius. Let us prove the following theorem.

Theorem (Kelvin). If a function $u(x)$ is harmonic in the region V the function

$$v(\xi)=\frac{1}{|\xi|}u\left(\frac{\xi_1}{|\xi|^2},\frac{\xi_2}{|\xi|^2},\frac{\xi_3}{\xi^2}\right) \tag{3.13}$$

will be harmonic in the region V'

Proof: Let us introduce the spherical coordinates r, θ and φ, with origin at the point $|x|=0$. Then, the point $\xi(r',\theta,\varphi)\in V'$, where $r'\equiv 1/r$, will be harmonically conjugate to the point $x(r,\theta,\varphi)$, $\left(r'\equiv\frac{1}{r}\right)$.Therefore, eq.(3.13) takes the form

$$v(r',\theta,\varphi)=ru(r,\theta,\varphi)=\frac{1}{r'}u\left(\frac{1}{r'},\theta,\varphi\right) \tag{3.14}$$

Let us first assume that the region V' does not contain point $r'=0$. Substituting the function V in the Laplace equation in spherical coordinates we obtain.

$$\Delta_\xi v=\frac{\partial}{\partial r'}\left(\frac{1}{r'},\theta,\varphi\right)=ru(r,\theta,\varphi)=\frac{1}{r'}u\left(\frac{1}{r'},\theta,\varphi\right),r'\equiv\frac{1}{r}. \tag{3.15}$$

and since

$$\frac{\partial}{\partial r'}=\frac{\partial r}{\partial r'}\frac{\partial}{\partial r}=-\frac{1}{r'^2}\frac{\partial}{\partial r}=-r^2\frac{\partial}{\partial r},$$

we obtain

$$\frac{\partial}{\partial r'}\left\{r'^2\frac{\partial}{\partial r'}\left[\frac{1}{r'}u\left(\frac{1}{r'},\theta,\varphi\right)\right]\right\}=r^2\frac{\partial^2}{\partial r^2}[ru(r,\theta,\varphi)]=r\frac{\partial}{\partial r}\left(r^2\frac{\partial u}{\partial r}\right), \tag{3.16}$$

so that

$$\frac{\partial}{\partial r}\left(r^2\frac{\partial u}{\partial r}\right)+\frac{1}{\sin\theta}\left(\frac{\partial}{\partial\theta}\sin\theta\frac{\partial u}{\partial\theta}\right)+\frac{1}{\sin^2\theta}\frac{\partial^2 u}{\partial\theta^2}=0 \qquad (3.17)$$

Since the function u is harmonic in the region V, this equation is identically satisfied when $x(r,\theta,\varphi)\in V$, that is when $\xi(r',\theta,\varphi)\in V'$. Consequently, the function $v(\xi)$ satisfies the Laplace eq.(3.15) when $\xi\in V'$. Then, as can easily be seen by direct differentiation, the existence and continuity of the derivatives of $u(x)$ in the region V imply the existence and continuity of the derivative of the same order of the function $v(\xi)$ in the region V'. Thus, the theorem is proven for the assumption that the point $r'=0$ does not belong to the region V'. This point is singular for the function

$$v=\frac{1}{r'}u\left(\frac{1}{r'},\theta,\varphi\right). \qquad (3.18)$$

Let us show that this is a removable singularity.

Suppose that ξ is an arbitrary point of the region V' that does not coincide with the point $r'=0$, and that ω is a sphere with center at the point $r'=0$ and radius so small that the point ξ lies outside the sphere. Then the region $V'-\omega$ does not contain the point $r'=0$ and, from what we have shown above, the function v is harmonic within this region and, in particular, harmonic at he point ξ. Consequently, the function v is harmonic at all points of some neighborhood of the point $r'=0$, except for this point itself (where it is not defined). By the preceding

lemma, as r' approaches zero the function v either remains bounded or increases at least as rapidly as $1/r'$, However, the latter is impossible. For it follows from eq .(3.14) that

$$r'v(r',\theta,\varphi)=u\left(\frac{1}{r'},\theta,\varphi\right). \tag{3.19}$$

As r' approaches zero, the function $u(1/r',\theta,\varphi)$ approaches a limit that is equal to its value at an infinitely distant point. But since the function u is harmonic by hypothesis, this limit is equal to zero, and, consequently.

$$\lim_{r'\to 0} r'v=0. \tag{3.20}$$

Thus, the function v is bounded in a neighborhood of its singular point and hence, it may be redefined so as to be harmonic throughout he entire region V'. This completes the proof of Kelvin's theorem.

A lemma on the behavior of a harmonic function at infinity follows from Kelvin's theorem:

A function u that is harmonic in an infinite region satisfies the inequalities

$$|u(x)|<\frac{A}{|x|},\left|\frac{\partial u}{\partial x_i}\right|<\frac{A}{|x|^2}\left(i=1,2,3,\ |x|=\sqrt{x_1^{\,2}+x_2^{\,2}+x_3^{\,2}}>r_0\right), \tag{3.21}$$

where A and r_0 are properly chosen constants.

Proof : Suppose that ξ is a point that is a harmonic conjugate of the point x. The function $v(\xi)=|x|u(x)$ is harmonic at the point $\xi=0$ and in some neighborhood

$|\xi| < \xi$ (on the basis of Kelvin's theorem) it is, therefore, bounded there. This implies the first of the inequalities (3.21) for $r_0 = 1/\in$, and for some value $A > A_0$, where A_0 is the maximum of the function $|v(\xi)|$ for $|\xi| < \in$. Furthermore , noting that for $a = 1$, formulation $|v(\xi)|$ for $|\xi| < \xi$. Furthermore, noting that, for $a = 1$, the formula

$$\frac{\partial}{\partial x_i} = \sum_{\alpha=1}^{3} \frac{\partial u}{\partial x_l} \frac{\partial}{\partial \xi_\alpha} = \frac{1}{|x|^2} \frac{\partial}{\partial \xi_i} - \frac{2x_i}{|x|^3} \sum_{\alpha=1}^{3} \frac{x_\alpha}{|x|} \frac{\partial}{\partial \xi_\alpha} \tag{3.22}$$

follows from eq .(3.7)), we obtain by direct differentiation

$$\frac{\partial u}{\partial x_i} = \frac{1}{|x|^2} \frac{\partial}{\partial \xi_i} |\xi| v(\xi) - \frac{2x_i}{|x|^3} \sum_{\alpha=1}^{3} \frac{x_\alpha}{|x|} \frac{\partial}{\partial \xi_\alpha} |\xi| v(\xi)$$

$$= \frac{1}{|x|^3} \frac{\partial v}{\partial \xi_i} + \frac{1}{|x|^2} \frac{\xi_i}{|\xi|} v - \frac{2x_i}{|x|^3} \sum_{\alpha=1}^{3} \frac{x_\alpha}{|x|} \left[\frac{1}{|x|} \frac{\partial v}{\partial \xi_\alpha} + \frac{\xi_\alpha}{|\xi|} v \right] \tag{3.23}$$

Since the ratios $x_j/|x|$ and ξ_j/ξ (where $j = 1, 2, 3$), and also (in the neighborhood $|\xi| < \xi$) the functions v and $\partial v/\partial \xi j$ are bounded, there exists a positive number A_i such that

$$\left| \frac{\partial u}{\partial x_i} \right| < \frac{A_i}{|x|^2}. \tag{3.24}$$

If, for A, we choose the greatest of the numbers A_0, A_j (where $j = 1, 2, 3$), we obtain all the inequalities (24).

The theorems and proofs given above will allow us to establish the uniqueness of

the solutions of the Laplace and Poisson equations. We do so in the next section .

3.4 Uniqueness of the Solutions to Boundary-Value Problems

Let us prove the uniqueness of the solution to Dirichlet's problem for the Laplace and Poisson equations. Let us suppose that Dirichlet's problem.

$$\Delta u = f \qquad \text{when} \qquad x \in V - FV, \tag{3.25a}$$

$$u = \psi \qquad \text{when} \qquad x \in FV, \tag{3.25b}$$

has two distinct solutions u_1 and u_2. Then, the difference $w = u_1 - u_2$ is harmonic in the w and vanishes on its boundary.

If the region V is bounded, we may immediately apply the extreme-value theorem. Inside the region V, the harmonic function w cannot have values either greater or less than its boundary value, which is zero. Therefore, it is equal to zero throughout the interior of the region; that is, the functions u_1 and u_2 coincide within the region in question. If the region V is infinite, we use Kelvin's theorem, setting

$$w^*(\xi) = |x|\, w(x), \tag{3.26}$$

where ξ is the point with coordinates

$$\xi_i \equiv x_i / |x| \tag{3.27}$$

The function $w^*(\xi)$ is harmonic in the bounded region V' (conjugate to the region V) and vanishes on its boundary because of the boundary conditions for the

function w.

Consequently, on the basis of the above, $w^*(\varepsilon)$ is equal to zero and hence the function. $w(x)=|\xi|w^*(\xi)$ is also equal to zero. This completes the proof.

It can be shown that the solution to Dirichlets' problem in question depend continuously on boundary condition. Suppose that u_1 and u_2 are solutions to two Dirichlet's problems for a single region, and that the boundary values of these solutions differ by not more that an amount ξ. Then, the function w, identically equal to u_1-u_2 is harmonic and differs from zero by no more than ε at points of the boundary of the region. If the region V is bounded, then, on the basis of the extreme-value theorem, the function u_1 and u_2 cannot differ from zero by more then ξ at an arbitrary point within the region.

Consequently, throughout the entire region, $|u_1-u_2|\leq\varepsilon$. From which the above assertion follows: If the region V is infinite, but the point $|x|=0$ does not belong to the region, them, by using Kelvin's-theorem we obtain the function $w^*(\xi)=|x|w(x)$, which is harmonic in the bounded region V' conjugate to the region V. The boundary values of the function w^* do not exceed $A\xi$, where A is a maximum values of the quantity $|x|$ on the boundary FV. Consequently from what we have shown, $w(x)<(A/B)\varepsilon$, where ξ is an element of V'.

Hence $w^*(\delta)<A\varepsilon$, where B is the smallest value of the quantity $|x|$ on the

boundary FV. Thus, the assertion is proven.

To examine Neumann's problem and the mixed problem, we use the identity

$$v\left(\frac{du}{dn}+\beta u\right)-u\left(\frac{dv}{dn}+\beta v\right)=v\frac{du}{dn}-u\frac{dv}{dn} \tag{3.28}$$

where β is an arbitrary continuous function. Using the notation $P \equiv \frac{d}{dn}+\beta$, and integrating both sides, we obtain Green's theorem in the form

$$\iint_{FV}(vPu - uPv)ds = \iiint_{V}(v\Delta u - u\Delta v)dV \tag{3.29}$$

where V is a bounded region. Setting one of the functions appearing in this formula equal to unity and the other equal to the square of the harmonic function we arrive at Dirichlet's formula.

$$\iiint_{v}\left[\left(\frac{\partial w}{\partial x_1}\right)^2+\left(\frac{\partial w}{\partial x_2}\right)^2+\left(\frac{\partial w}{\partial x_3}\right)^2\right]dV=\iint_{FV}wPwdS-\frac{1}{2}\iint_{FV}\beta w^2 dS \tag{3.30}$$

We shall use this formula to establish the conditions for uniqueness of the solutions to the interior mixed problem and the interior Neumann problem for both Laplace and Poisson equations.

With the notation (3.13), both these problems can be written in the same form

$$\Delta u = f \quad \text{when } x \in V - FV \tag{3.31a}$$

$$Pu = \psi \quad \text{when } x \in FV \tag{3.31b}$$

If β is not identically equal to zero, eq .(3.31a) corresponds to the mixed problem, and for β identically equal to zero, if refers to the Neumann problem.

Let us suppose that the problem (3.31a) has two district solutions u_1 and u_2, that are continuous and have continuous first derivatives throughout the region V. Then their difference $w = u_1 - u_2$ is a solution to the homogeneous boundary problem for the Laplace equation

$$\Delta w = 0 \quad \text{when } x \in V - FV \tag{3.32a}$$

$$Pw = 0 \quad \text{when } x \in FV \tag{3.32b}$$

which satisfies the same continuity conditions. Then, for non-negative β, it follows from Dirichlet's formula that

$$\iiint_V \left[\left(\frac{\partial w}{\partial x_1} \right)^2 + \left(\frac{\partial w}{\partial x_2} \right)^2 + \left(\frac{\partial w}{\partial x_3} \right)^2 \right] dV \leq 0 \tag{3.33}$$

since all the terms in the integrand are non-negative, and since the expression itself, by hypothesis, continues, it follows that $\partial w / \partial x_i = 0$ (for $i = 1, 2, 3$) that is $w = u_1 - u_2 =$ constant.

To determine the admissible values of the constant of the right side of this equation, let us turn to the boundary condition for the homogeneous problem. If β is identically equal to zero (the Neumann problem), any constant satisfies the boundary condition. Consequently, any constant is a solution to the homogeneous Neumann problem, and therefore, the solution to the homogeneous Neumann problem is determined except for an arbitrary constant However, if β is different from zero for at least a portion of the boundary FV , then this constant will be

equal to zero. that is, the solution to the mixed problem is unique.

3.5 The Fundamental solutions to Laplace's equation. The basic formula in the theory of harmonic functions

The function

$$\frac{1}{r}=\frac{1}{\sqrt{\sum_{j=1}^{3}(\xi_j-x_j)^2}} \tag{3.34}$$

where ξ_j and x_j (for $j=1,2,3$) are the coordinates of two point ξ and x satisfies Laplace's equation for $\xi \neq x$. Since the expression $1/r$ is symmetric with respect to coordinates of the points ξ and x, this expression is valid under differentiation with respect to coordinates both of the point ξ and of the point x.

At $\xi = x$, the function $1/r$ has an infinite discontinuity.

If a function $\varphi(\xi,x)$ is harmonic in a region V with respect to the coordinates of the point ξ and if it and its first derivatives are continuous, we shall call the function.

$$L(\xi,x)=\frac{1}{4\pi}\left[\frac{1}{r}+\varphi(\xi,x)\right] \tag{3.35}$$

the fundamental solution to Laplace's equation in the region V.

By using the properties of fundamental solutions we can derive some important integral formulae relating to the value of an arbitrary sufficiently smooth

function at an arbitrary point (within or on the boundary of the domain of its definition) with the set of values of this function and its normal derivatives or the boundary of the region being considered.

Suppose V is a bounded region when a point x lies outside the region V, the fundamental solution $L(\xi,x)$ is harmonic in this region. Therefore, by setting $v(\xi)=L(\xi,x)$ in Green's theorem we obtain.

$$\iint_{FV}\left(L\frac{du}{dn}-u\frac{dl}{dn}\right)dS_{\xi}=\iiint_{V}l\Delta udV_{\xi}, \qquad (3.36)$$

$$x\in R_E-V$$

where R_E denotes all space and the point x is treated as a parameter. When the point x lies within the region V, we way apply Green's theorem to the region $V-\Omega_{\varepsilon}$ where Ω_{ε} is a sphere within the region V of arbitrary small radius ε with the centre at a point x. Here instead of the relationship (3.18) we obtain

$$\iint_{\mp V}\left(L\frac{du}{dn}-u\frac{dL}{dn}\right)dS_{\xi}=\iiint_{V-\Omega_{\varepsilon}}LdudV_{\xi}-\iint_{J\Omega_{\varepsilon}}L\frac{du}{dn}dS_{\xi}+\iint_{\mp\Omega_{\varepsilon}}u\frac{dl}{dn}dS_{\xi} \qquad (3.37)$$

As ε approaches zero, the integral

$$\iiint_{V-\Omega_{\varepsilon}}LdudV_{\xi} \qquad (3.38a)$$

approaches the improper integral

$$\iiint_{V}L\Delta udV_{\xi} \qquad (3.38b)$$

if this improper integral exists. The integral

$$\iint_{\mp\Omega_\varepsilon} L\frac{du}{dn}dS_\xi \tag{3.38c}$$

approaches zero because the derivative du/dn is continuous (by the assumption made in the derivation of Green's theorem) and therefore bounded, and the function $L(\xi,x)$ increases on $F\Omega_\varepsilon$ as $1/\varepsilon$ whereas the area of the surface $F\Omega_\varepsilon$ decreases as ε^2.

Let us examine the behavior of the integral of udL/du. From eq.(3.35)

$$\iint_{F\Omega_\varepsilon} u\frac{dL}{dn}dS_\xi = \frac{1}{4\pi}\iint_{F\Omega_\varepsilon} u\frac{d\varphi}{dn}dS_\xi + \frac{1}{4\pi}\iint_{F\Omega_\varepsilon} u\frac{d}{dn}\left(\frac{1}{r}\right)dS_\xi \tag{3.39}$$

The first of the integrals on the right side vanishes as ε approaches zero because the integrand is bounded. By using the fact that

$$F\Omega_\varepsilon\frac{d}{dn} = -\frac{d}{dr}. \tag{3.40}$$

On the surface of the sphere, we can transform the second integrand, since the outward normal to the boundary of the region $V-\Omega_\varepsilon$ is directed along the radius r within the sphere Ω_ε. This yields

$$\frac{1}{4\pi}\iint_{F\Omega\varepsilon} u\frac{d}{dn}\left(\frac{1}{r}\right)dS\xi = \frac{1}{4\pi}\iint_{F\pi}\frac{u}{r^2}dS_\xi = \frac{1}{4\pi\varepsilon^2}\iint_{I\Omega\varepsilon} udS_\xi \tag{3.41}$$

By the mean-value theorem,

$$\iint_{F\Omega\varepsilon} udS_\xi = u_{av}\iint_{F\Omega_\varepsilon} dS_\xi \tag{3.42}$$

where u_{av} is the value of the function u at some point belonging to the sphere Ω_{ϵ}.

Noting that the integral $\iint_{F\Omega\varepsilon} dS_{\xi}$

is equal to the area $4\pi\varepsilon^2$ of the surface $F\Omega_{\varepsilon}$ and that, as ε approaches zero, the value of u_{av} approaches $u(x)$ since the function u is continuous we obtain

$$\lim_{\varepsilon\to 0}\iint_{\mp\Omega} u\frac{dL}{dn}dS_{\xi} = \lim_{\varepsilon\to 0}\frac{u_{ar}}{4\pi\varepsilon^2}\iint_{\mp\Omega\varepsilon} ds_{\xi} = \lim_{\varepsilon\to 0} u_{av} = u(x). \tag{3.43}$$

Using the values of these limits, we finally obtain

$$\iiint_{FV}\left(L\frac{du}{dn} - u\frac{dL}{dn}\right)dS_{\varepsilon} = \iiint_{V} L\Delta u dv_{\xi} + u(x)(x \in V - FV) \tag{3.44}$$

Let us assume, finally that the point x is located on the boundary of the surface Fv. Then, by applying Green's theorem to the region $V-\Omega_{\varepsilon}'$, where Ω_{ε}' is the portion of the surface Ω_{ε} (of small radius $\in$ with the center at x) that lies on the region V, we obtain

$$\iint_{FV-\omega_{\varepsilon}}\left(L\frac{du}{dn} - u\frac{dL}{dn}\right)dS_{\xi} = \iiint_{V-\Omega_{\varepsilon}^{1}} L\Delta u dv - \iint_{\omega_{\varepsilon}^{1}} L\frac{du}{dn}dS_{\varepsilon} + \iint_{\omega\varepsilon} u\frac{dL}{dn}dS_{\xi} \tag{3.45}$$

where ω_{ε} is that part of the bounding surface FV lying in the sphere $\Omega\varepsilon$ and ω_{ε}^{1} is that part of the surface of the sphere $\Omega\varepsilon$ lying in the region V As ε approaches zero, the integral on the left side of this equation approaches an improper integral over FV. For its value, we take the integral on the right side which we compute by using the reasoning of the proceeding case, with the exception that now we have in

eq.(3.43), instead of the integral.

$$\iint_{F\Omega\varepsilon} dS_{\xi} \tag{3.46a}$$

the integral

$$\iint_{\omega'\varepsilon} dS_{\xi} \tag{3.46b}$$

which is equal to the area of that portion of the surface of the sphere Ω_{ε} that lies in the region V. Let us introduce at the point x a local cartesian coordinate system, $\varsigma_1, \varsigma_2, \varsigma_3$ with the third axis directed along the outward normal to the surface Fv at the point x. By hypothesis, within some sphere with centre at the point x the equation of the surface Fv can be written in the form

$$\varsigma_3 = f(\varsigma_1, \varsigma_2), \tag{3.47}$$

where the function f and its first-order derivatives are continuous and vanish at the point x. Therefore, from the definition of a differentiable function, throughout some neighborhood of the point x,

$$\varsigma_3 = h_1\varsigma_1 + h_2\varsigma_2 \tag{3.48}$$

where the quantities h_1 and h_2 vanish simultaneously with $\varsigma_1\ \varsigma_2$. Let us introduce spherical coordinates,(r, θ, φ), by setting

$$\varsigma_1 = r\sin\theta\cos\varphi, \quad \varsigma_2 = r\sin\theta\sin\varphi, \quad \varsigma_3 = r\cos\theta \tag{3.49}$$

Substituting these expressions in the relations that we have found, we obtain

$$\cos\theta = h_1\sin\theta\cos\varphi + h_2\sin\theta\varphi = h(r, \theta, \theta) \tag{3.50}$$

where h is a function that is bounded and vanishes simultaneously with r, and where θ is the angular coordinate of the point on the surface Fv. By using this expression, we arrive at the following evaluation of the integral.

$$\frac{1}{4\pi\ \in^2}\iint_{\omega_\in} dS_\xi = \frac{1}{4\pi\ \in^2}\iint_{\omega_\in} r^2 \sin\theta'\, d\theta' d\varphi' = \frac{1}{4\pi}\int_0^{2\pi} d\varphi' \int_0^{\theta} \sin\theta' d\theta'$$

$$= \frac{1}{4\pi}\int_0^{2\pi} d\varphi' \int_0^{\frac{1}{2}\pi} \sin\theta' d\theta' + \frac{1}{4\pi}\int_0^{2\pi} d\varphi' \int_{\frac{1}{2}\pi}^{\theta} \sin\theta' d\theta'$$

$$= \frac{1}{2} + \frac{1}{4\pi}\int_0^{2\pi} d\varphi' [-\cos\theta']_{\frac{1}{2}\pi}^{\theta} = \frac{1}{2} + \frac{1}{4\pi}\int_0^{2\pi} h(\in,\theta,\varphi') d\varphi$$

$$= \frac{1}{2} + H(\in), \tag{3.51}$$

where, $$H(\in) = \frac{1}{4\pi}\int_0^{2\pi} h(\in,\theta,\varphi') d\varphi' \tag{3.52}$$

is a bounded function that vanishes simultaneously with $\in$. Therefore,

$$\lim_{\varepsilon\to 0}\iint_{\omega\in} u\frac{dL}{dn} dS_\xi = \lim_{\varepsilon\to 0}\frac{u_{av}}{4\pi\ \in^2}\iint_{\omega_\in} dS_\xi = \lim_{\varepsilon\to 0} u_{av}\left[\frac{1}{2} + H(x)\right] = \frac{1}{2}u(x) \tag{3.53}$$

which leads us to the relation

$$\iint_{FV}\left(L\frac{du}{dn} - u\frac{dL}{dn}\right) dS_\xi = \iiint_V L\Delta u dV_\xi + \frac{1}{2}u(x) \quad (x \in FV) \tag{3.54}$$

by combining eqs (3.36), (3.44), and (3.54), we may write

$$\iiint_{FV}\left(L\frac{du}{dn}-u\frac{dL}{dn}\right)dS_\xi=\iiint_V L\Delta u dV_\xi=\begin{cases}0 & \text{when } x\in R_E-V,\\ \frac{1}{2}u(x) & \text{when } x\in FV,\\ u(x) & \text{when } x\in V-FV\end{cases} \tag{3.55}$$

If the function u is harmonic in the region V, then eq .(3.23) take

$$\iint_{FV}\left(L\frac{du}{dn}-u\frac{dL}{dn}\right)dS_\xi=\begin{cases}0 & \text{when } x\in R_E-V,\\ \frac{1}{2}u(x) & \text{when } x\in FV,\\ u(x) & \text{when } x\in V-FV\end{cases} \tag{3.56}$$

This relationship is called the basic formula in the theory of harmonic functions. It can be extended to infinite regions. Suppose that V is an infinite region with a finite boundary FV, and that **V*** is that portion of the region V lying within a sphere Ω of finite radius r containing the boundary FV. By applying eq .(3.56) to the region **V*** we arrive at an equation whose left side will differ from that of eq .(3.56) only in by addition of the integral

$$\iint_{F\Omega}\left(L\frac{du}{dn}-u\frac{dL}{dn}\right)dS_\xi \tag{3.57}$$

With unbounded increase in the radius of the sphere, this integral approaches zero because the behavior of a harmonic function at infinity and from the definition of a fundamental solution $L(\xi,x))$, the integrand here decreases as $1/r^3$ whereas the area of the surface FV of the sphere Ω increases only as r^2. Taking the limit as r approaches ∞, we again obtain the formula

$$\iint_{FV}\left(L\frac{du}{dn}-u\frac{dL}{dn}\right)dS_{\xi}=\begin{cases}0 & \text{when} \quad x\in R_E-V,\\ \frac{1}{2}u(x) & \text{when} \quad x\in FV,\\ u(x) & \text{when} \quad x\in V-FV,\end{cases} \tag{3.58}$$

which coincides with eq.(3.56) for bounded regions.

By using eqs (3.56) and (3.58), we shall show that, within the region where it is harmonic, an arbitrary harmonic function is differentiable infinitely many times. Let us set

$$L(\xi,x)=\frac{1}{4\pi}\frac{1}{r} \tag{3.59}$$

The fundamental solution $(1/4\pi)(1/r)$ in an arbitrary region not containing the point $\xi = x$ is differentiable infinitely many times with respect to the coordinates of the point x, and each time, the result of the differentiation is a bounded function of the variable ξ. If x is an interior point of the region V, then ξ will be different from x when ξ is an element of FV. Consequently, the integrals in eq.(3.56) and eq.(3.58) can be differentiated with respect to the coordinates of the point x (treated as parameters) infinitely many times. This proves the assertion for the case when the harmonic function u and its not continuous, this assertion remains valid because, in eqs (3.56) and (3.58), we may change from integration over the surface FV to integration over the S, which lies entirely within the region V and which contains the point x. Since, within the region where it is harmonic, every harmonic function is differentiable twice, the formula containing the integral over the surface S will be meaningful and, consequently, it again implies

differentiability infinitely many times of the function $u(x)$.

Suppose that Ω is a sphere of radius a with center at the point x and that Ω lies entirely within the region where the function u is harmonic on the surface of the sphere Ω,

$$d/dn = d/dr \tag{3.60}$$

As before, we set

$$L(\xi, x) = \frac{1}{4\pi}\frac{1}{r}. \tag{3.61}$$

Then, on the basis of eq. (3.14), eq. (3.24) takes the form

$$\frac{1}{4\pi a^2}\iint_{F\Omega} u dS_\xi = u(x); \tag{3.62}$$

that is, the mean arithmetic value of a harmonic function on the surface of a sphere is equal to it value at the center of the sphere. This assertion is known as the mean-value theorem for harmonic functions.

CHAPTER FOUR

ELECTROSTATIC POTENTIAL IN ACH CHANNEL

4.1 Introduction

In this chapter we focus on electrostatic interactions between biological macromolecules and how these interactions affect the flow of ions through the ACh channel. Two of the key concepts that come into play are "electronic charge" and "electric potential".

The flow of charges in a medium is usually associated with the source or sinks which produces the force field. For a unit area, the charge density ρ defines the magnitude of the charge in a closed region and is described by Gauss' Law which states: "The net flux through any closed surface in proportional to the net charge contained within the closed surface." The point charges, however, interact according to Coulomb's Law, which states: "The electrostatic force acting between two charges is proportional to the charge on each and inversely proportional to the square of their separation". The presence of an electronic charge density ρ, creates a negative electric potential ,Φ.

This statement is usually expressed by the equation.

$$\nabla^2\Phi = -\rho/\varepsilon \tag{4.1}$$

where ε is a constant in this case called dielectric constant of the medium.

4.2The Poisson Equation Formalism

The Poisson equation formalism is used to describe a relationship between the net charge density of a system of continuous distribution of charge on an ion and the system's potential Φ. As stated in the introduction, such a potential derives from sources or sinks of the flow of charges producing the force and it is normally expressed in the form of a second order partial differential equation:

$$\nabla^2\Phi = -\frac{4\pi\rho}{\varepsilon} \tag{4.2}$$

with appropriate boundary conditions. The typical boundary conditions include

(i) the potential being assigned a known value at one of the boundaries, that is $\Phi(r_0) = \Phi_0$,

(ii) zero flux and

(iii) the potential being continuous at the channel solvent interface. Here, the standard continuity equations are given by:

$$\Phi_i = \Phi_e, \in_e \nabla\Phi_i \cdot \hat{n} = \in_e \nabla\Phi_e \cdot \hat{n}, \tag{4.3}$$

where the subscripts that denote the inside and outside of the channel respectively and $\hat{n}$ is the unit outward normal to the surface. The related homogeneous Laplace equation is equivalent to the requirement that the potential does not attain any minimum or maximum value inside the region of interest.

4.3 Cylindrical Approximation

The cylinder is used as convenient approximation to the ACh receptor channel. The choice of cylindrical geometry to represent the ACh channel has some advantages. These include the simplification of the mathematical calculations of the channel potential and subsequent model analyses. For example, by using cylindrical geometry, the separation for the Laplace equation is assured and axi-symmetry is guaranteed. Consequently, an analytical solution to the shape of the channel on the potential barrier and the electrostatic field on ion moving within that geometry encounter, we will examine the solution to the Poisson equation inside this overly simplified model of channel geometry. The cylinder is represented by the parametric equations with parameters , (r,θ,z), as

$$\begin{cases} x &= r\cos\theta \\ y &= r\sin\theta \\ z &= z \end{cases} \tag{4.4}$$

The Laplace equation in this domain is given by:

$$\nabla^2\Phi = \frac{\partial^2\Phi}{\partial r^2} + \frac{1}{r}\frac{\partial\Phi}{\partial r} + \frac{1}{r^2}\frac{\partial^2\Phi}{\partial\theta^2} + \frac{\partial^2\Phi}{\partial z^2} = 0 \tag{4.5}$$

(See Appendix 4)

To seek the solution of this equation we use the method of separation of variables.

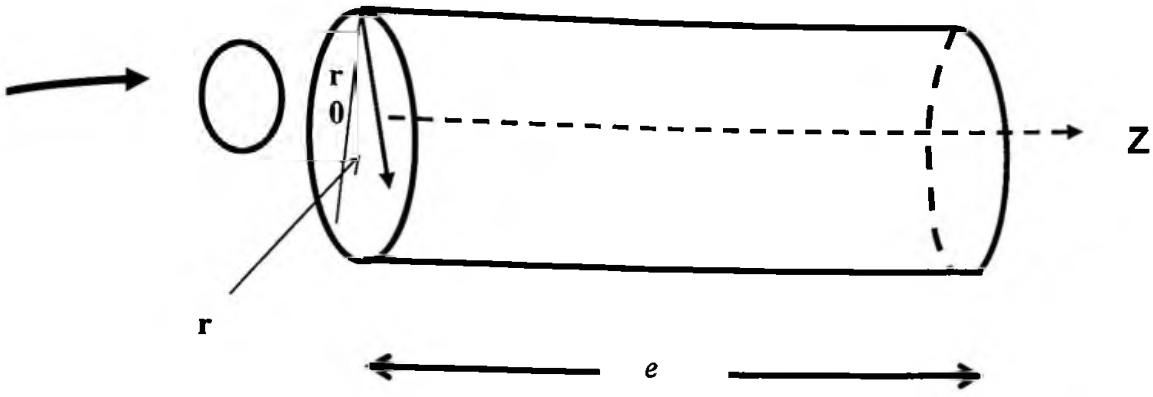

Fig. 4.1 Cylindrical geometry – an approximation to the ACh channel.

The equation separates as:

$$\Phi = \Theta(\theta)R(r)Z(z) \tag{4.6}$$

where $\Theta(\theta), R(r), Z(z)$ satisfy the equations:

$$\frac{d^2\Theta}{d\theta^2} + p^2\theta = 0 \tag{4.7}$$

$$\frac{1}{r}\frac{d}{dr}\left(r\frac{dR}{dr}\right) + \left(k^2 - \frac{p^2}{r^2}\right)R = 0 \tag{4.8}$$

$$\frac{d^2Z}{dz^2} - k^2Z = 0 \tag{4.9}$$

Here, p and k are real numbers. For a cylinder of length l and radius r_0 with $\Phi = \Phi_0$ at $z = 0$ and the potential being zero at the other faces, the analytical solution to the Laplace equation within the cylindrical domain is given by

$$\Phi(r,\theta,z)=\sum_{m,n}\{\int_0^{2\pi}\cos[m(\theta-\theta')]\,d\theta'\int_0^{ro}\Phi_0(u,\theta')J_m\left(\frac{\pi\beta_{mn}u}{r_0}\right)udu\}$$

(4.10)

$$\times\left\{\frac{\in_m \sinh\left[(\pi\beta_{mn}/r_0)(l-z)\right]}{\pi\left[r_o J_{m+1}(\pi\beta_{mn})\right]^2\sinh\left[(\pi\beta_{mn}/r_0)\right]}\right\}J_m\left(\frac{\pi\beta_{mn}r}{r_0}\right)$$

(see appendix 1 for further details)

where J_m is the Bessel function of order m, and $n=1,2\ldots,$ labels the eigenvalues, θ' and u are dummy variables and β_{mn} are the eigenvalues of equation such that $\beta_{m(n+1)}>\beta_{mn}$ and $\beta=\frac{p^2}{k^2}$ is a nonnegative real number .

The corresponding Poisson equation is given by:

$$\nabla^2\Phi=\frac{\partial^2\Phi}{\partial r^2}+\frac{1\partial\Phi}{r\partial r}+\frac{1\partial^2\Phi}{r^2\partial\theta^2}+\frac{\partial^2\Phi}{\partial z^2}=-\frac{4\pi\rho}{\varepsilon},\qquad(4.11)$$

where the initial conditions are similar to those of Laplace equation. Applying one of the standard methods of solution of nonhomogenous partial differential equations, the solution to the Poisson equation can be given as:

$$\Phi(r,\theta,z)=\sum_{n,m}\frac{\left(32/\pi^3\right)\beta_{0m}(2n+1)}{J_1\left(\pi\beta_{0m}\left\{\left[(2n+)/l\right]^2+\left(\beta_{0m}/r_0\right)^2\right\}\right)}$$

$$x\sin\left[\frac{\pi z}{l}(2n+1)J_0\left[\frac{\pi\beta_{0m}r}{r_0}\right]\right]\qquad(4.12)$$

where the parameters are defined in Appendix 2 .

4.4 Toroidal Approximation

An improvement on the cylindrical channel geometry is the adoption of a toroidal structure (see for example, Kuyucak et al, 1998).

The toroidal coordinates (η, μ, ϕ) (see figures 4.1b and 4.1c) are related to the Cartesian ones through the following set of equations (Morse and Feshbach, 1953)

$$x = \frac{a \sinh \mu \cos \phi}{\cosh \mu - \cos \eta}, \quad y = \frac{a \sinh \mu \sin \phi}{\cosh \mu - \cos \eta} \quad z = \frac{a \sin \eta}{\cosh \mu - \cos \eta} \tag{4.13}$$

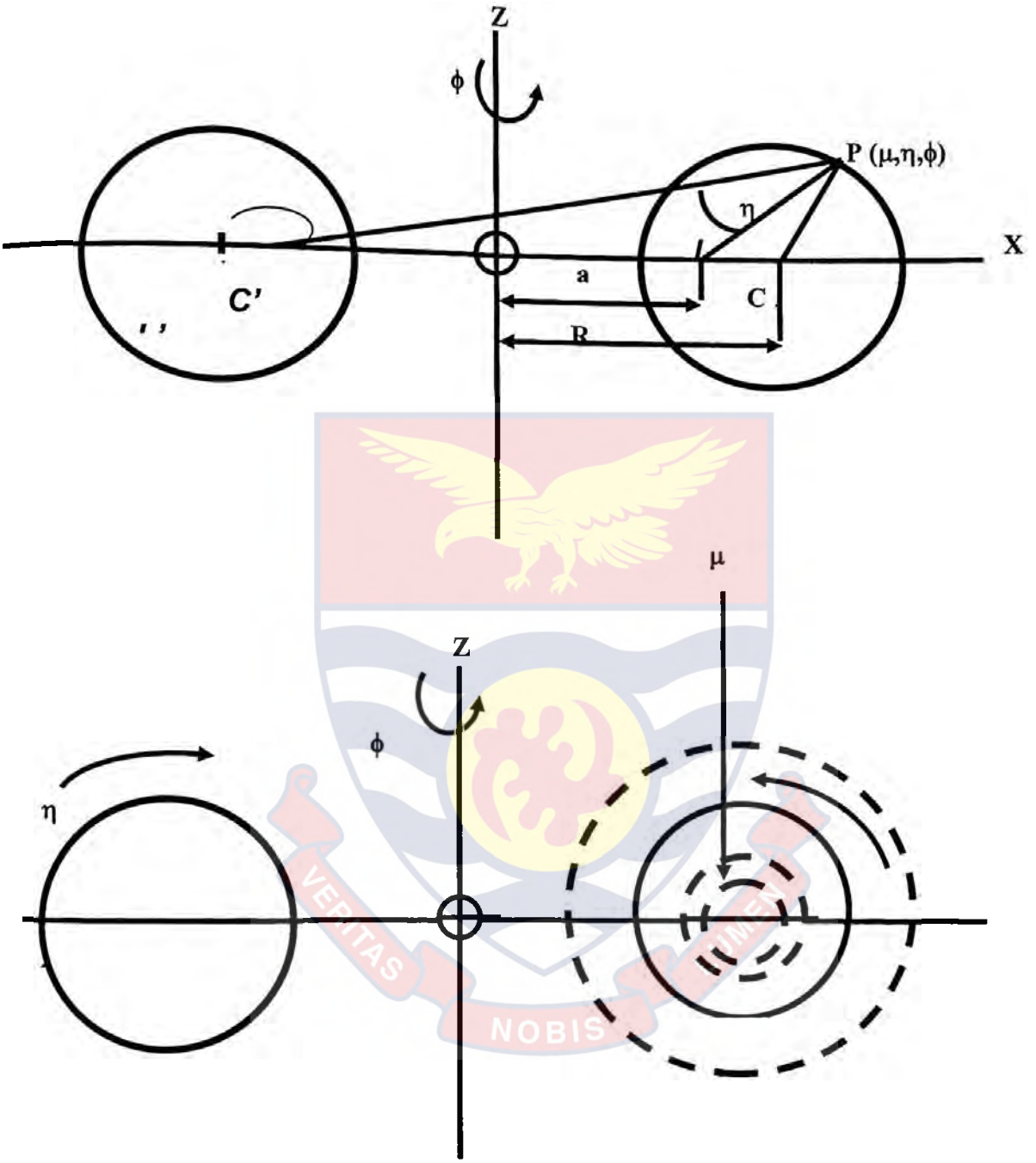

Figure 4.1b. The torus is generated by rotating the two circles about the z-axis through two right angles. This is illustrated in the first figure. The second figure shows how the three coordinates defining the toroidal system are related.

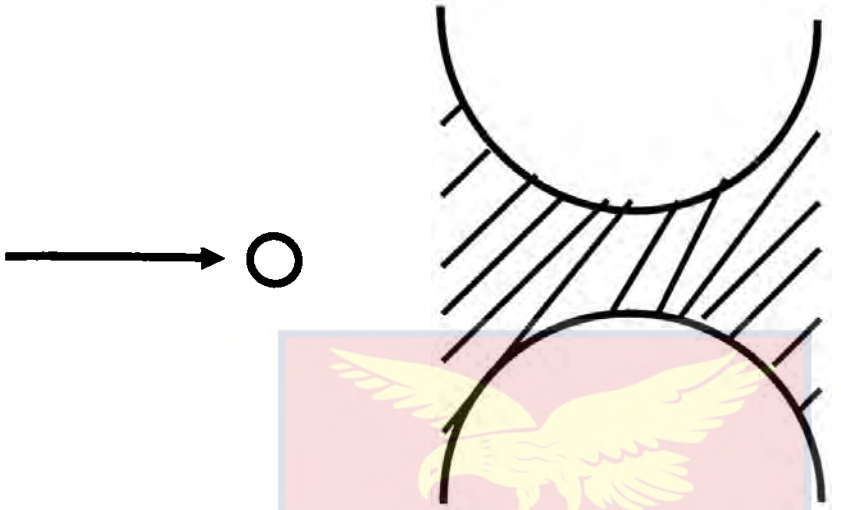

Figure 4.1c: A cross-section of the toroidal catenary. The channel is formed outside the 'doughnut shape'. The solution to the Poisson equation here, is therefore an outer solution

In the $x-z$ plane, the circle describing the toroidal surface will intersect the positive x axis twice, x_1 at $\eta = 0$ and x_2 at $\eta = \pi$. Thus the radius r of the torus is related to the toridal coordinates by the expression ,

$$x_1 - x_2 = \frac{a\sinh\mu_1}{\cosh\mu_1 - 1} - \frac{a\sinh\mu_1}{\cosh\mu_1 + 1} \qquad (4.14)$$

$$= \frac{2a\sinh\mu_1}{\cosh^2\mu_1 - 1} = \frac{2a}{\sinh\mu_1} = 2r$$

Similarly, the distance from the origin to the centre of the torus R can be expressed in terms of the toroidal coordinates as

$$R = x_2 + \frac{x_1 - x_2}{2} = a\left(\frac{\sinh\mu_1}{\cosh\mu_1 + 1} + \frac{1}{\sinh\mu_1}\right)$$

$$= a\frac{\cosh\mu_1}{\sinh\mu_1} = a\coth\mu_1 \qquad (4.15)$$

Thus, as η changes from 0 to 2π, constant μ_1 follows a circle of the minor radius, $r = a/\sinh\mu_1$, centered at the major radius $R = a\coth\mu_1$. By rotating the two circles around the perpendicular z axis, the full toroidal boundary is generated.

We note that the ratio between the minor and major radii, $r/R = 1/\cosh\mu_1$. is independent of a and determines the diameter of the constricted region of the model channel. For $\mu = 0$, both r and R are infinite, and the circle becomes the z axis. In the opposite limit, $\mu = \infty$, the major and minor radii coincide, i. e., $R = a$ and $r = 0$, and the toroid becomes a ring of radius r around the z axis.

Solution of Laplace's equation in toroidal coordinates is given in terms of the trigonometric functions for η and ϕ and the toroidal harmonics (Legendre functions of half-order) $P^m_{n-1/2}(\cosh\mu)$, $Q^m_{n-1/2}(\cosh\mu)$. The most general solution can be written as

$$\varphi = f(\mu,\eta)\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}\left[A_{nm}\,Q^m_{n-1/2}(\cosh\mu) + B_{nm}\,p^m_{n-1/2}(\cosh\mu)\right] \qquad (4.16)$$

$$\times\cos n(\eta-\eta_{nm})\cos m(\phi-\phi_{nm})$$

where

$$f(\mu,\eta) = \sqrt{\cosh\mu-\cos\eta} \qquad (4.17)$$

and the coefficients $A_{nm}, B_{nm}, \eta_{nm}, \phi_{nm}$ are to the determined from boundary conditions. (See Appendix 3 for further details).

The potential due to a point charge q at $r_0 = (\mu_0,\eta_0,\phi_0)$ is given by (Morse and Feshback, 1953)

$$\frac{q}{|r-r_0|} = \frac{q}{\pi a} f(\mu,\eta) f(\mu_0,\eta_0)\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}(2-\delta_{n0})\;(2-\delta_{m0})$$

$$\frac{\Gamma(n-m+1/2)}{\Gamma(n+m+1/2)}\times\cos n(\eta-\eta_0)\cos m(\phi-\phi_0)$$

$$\begin{Bmatrix} p^m_{n-1/2}(\cosh\mu)\,Q^m_{n-1/2}(\cosh\mu_0) & \mu<\mu_0 \\ p^m_{n-1/2}(\cosh\mu)\,P^m_{n-1/2}(\cosh\mu_0) & \mu<\mu_0 \end{Bmatrix} \qquad (4.18)$$

The change in the μ solution reflects the fact that $P^m_{n-1/2}$ diverges as $\mu\to\infty$ and $Q^m_{n-1/2}$ diverges as $\mu\to 0$. Solution of Poisson's equation for the system of a point

charge outside the toroidal boundary $\mu = u_1 > \mu_0$, with dielectric constants ϵ_1 and ϵ_2 inside the torus, can be found by superposing the potentials in Eqs. (4.4) and 4.6). As usual in such boundary value problems, the ϕ solutions are decoupled, and the phases ϕ_{nm} in eq.(4. 4) must be coherent with ϕ_0, so that $\phi_{nm} = \phi_0$ for all n,m. The same argument, however, does not hold for the η solutions. Because of the square root factor of f eq. (4.5), there is coupling between different coefficients and the phase factors η_{nm} are not necessarily coherent with η_0. This is a distinctive feature of the toroidal coordinates, and complicates solutions of electrostatic problems in comparison with other coordinate systems. With these caveats, the superposed potential can be written as.

$$\varphi_{in} = f(\mu,\eta)\sum_{n=-\infty}^{\infty}\sum_{m=0}^{\infty} A_{nm} Q^m_{n-1/2}(\cosh\mu) \cdot \exp[in(\eta-\eta'_{nm})]\cos m(\phi-\phi_0) \qquad (4.19)$$

$$\varphi_{out} = f(\mu,n)\sum_{n=-\infty}^{\infty}\sum_{m=0}^{\infty}\left[B_{nm}P^m_{n-1/2}(\cosh\mu)\exp[in(\eta-\eta''_{nm})]\right. + C_{nm}Q^m_{n-1/2}(\cosh\mu)\exp[\eta-\eta_0]\left.\right] .\cos m(\phi-\phi_0) \qquad (4.20)$$

where

$$C_{nm} = \frac{1}{4\pi\,\epsilon_0\epsilon_1}\frac{q}{\pi a} f(\mu_0,\eta_0)(2-\delta_{m0})\frac{\Gamma(n-m+1/2)}{\Gamma(n+m+1/2)} .P^m_{n-1/2}(\cosh\mu_0) \qquad (4.21)$$

are constant coefficients . In eq. (4.20), we used the $\mu > \mu_0$ solution for the point charge eq.(4.19) as is the appropriate one for the boundary at $\mu > \mu_1$. Also, we

replaced the cosines with exponentials for the η solution, because it simplifies the boundary matching.

Applying the usual boundary conditions at $\mu = \mu_1$,.

$$\varphi_{in} = \varphi_{out}, \epsilon_2 \frac{\partial \varphi_{in}}{\partial(\cosh \mu)} = \epsilon_1 \frac{\partial \varphi_{out}}{\partial(\cosh \mu)} \tag{4. 22}$$

we obtain the following equations for every m:

$$\sum_{n=-\infty}^{\infty} A_{nm} Q \exp[in(\eta - \eta'_{nm})]$$

$$= \sum_{n=-\infty}^{\infty} [B_{nm} P \exp[in(\eta - \eta''_{mn})] + C_{nm} Q \exp[in(\eta - \eta_0)]] \tag{4.23}$$

$$\epsilon_2 \sum_{n=-\infty}^{\infty} A_{nm} (fQ' + f'Q) \exp[in(\eta - \eta'_{nm})]$$

$$= \epsilon_1 \sum_{n=-\infty}^{\infty} [B_{nm} (fP' + f'P) \exp(\eta - \eta'_{nm})]$$

$$+ C_{nm} (fQ' + f'Q) \exp[in(\eta - \eta_0)]] \tag{4.24}$$

Here we have introduced the compact notation for the constants,

$P = P^m_{n-1/2}(\cosh \mu_1)$, $Q = Q^m_{n-1/2}(\cosh \mu_1)$ and $f = f(\mu_1, \eta)$. Similarly, the primes over $P, Q,$ and f denote derivatives with respect to $\cosh \mu$ evaluated at $\mu = \mu_1$.

These equations can be further simplified by introducing the complex coefficients

$$A'_{nm} = A_{nm} \exp[-in\eta'_{nm}], B'_{nm} = B_{nm} \exp[-in\eta''_{nm}]$$

$$C'_{nm} = C_{nm} \exp(-in\eta_0) \tag{4.25}$$

Substituting the above coefficients in Eqs. (4.23) and (4.24), we obtain

$$\sum_{n=-\infty}^{\infty} A'_{nm} Q \exp[in\eta] = \sum_{n=-\infty}^{\infty} [B'_{nm} P + C'_{nm} Q] \exp[in\eta] \tag{4.26}$$

$$\epsilon_2 \sum_{n=-\infty}^{\infty} A'_{nm} (fQ' + f'Q) \exp[in\eta]$$

$$= \epsilon_1 \sum_{n=-\infty}^{\infty} [B'_{nm} (fP' + f'P) \exp[in\eta] \tag{4.27}$$

$$+ C'_{nm} (fQ' + f'Q) \exp[in\eta]$$

eq (4.26) now holds for each n, and hence we can solve for B'_{nm} in terms of A'_{nm} :

$$B'_{nm} = (A'_{nm} - C'_{nm}) Q/P \tag{4.28}$$

Substituting B'_{nm} in eq (4.27) and collecting similar terms gives

$$\sum_{n=-\infty}^{\infty} A'_{nm} [\epsilon_2 (fQ' + f'P) Q/P] \exp[in\eta]$$

$$= \epsilon_1 \sum_{n=-\infty}^{\infty} C'_{nm} f (Q' - P'Q/P) \exp(in\eta) \tag{4. 29}$$

Using $f' = 1/2f$ and substituting back $f^2 = \cosh \mu_1 - \cos \eta$ eq. (4.29) can be put in the form

$$2(\cosh \mu_1 - \cos \eta) \sum_{n=-\infty}^{\infty} A'_{nm} (\epsilon_2 Q' - \epsilon_1 P'Q/P) \exp(in\eta)$$

$$+ (\epsilon_2 - \epsilon_1) \sum_{n=-\infty}^{\infty} A'_{nm} Q \exp[in\eta] \tag{4.30}$$

$$= 2\epsilon_1 (\cosh \mu_1 - \cos \eta) \sum_{n=-\infty}^{\infty} C'_{nm} (Q' - P'Q/P) \exp[in\eta]$$

Notice that the $\cos\eta$ factors in the front leads to coupling of neighboring coefficients, so that eq (4.30) cannot be solved trivially, as typically encountered in boundary value problems involving spherical or cylindrical coordinate systems. Fourier analysis of the series in eq. (4.30) in η (i.e., multiplying by either $n'\eta$ or $\cos n'\eta$ integrating from $0-2\pi$ gives

$$\sum_{n=-\infty}^{\infty}\left[\left(2\cosh\mu_1(\epsilon_2\, Q'-\epsilon_1\, P'Q/P)+(\epsilon_2-\epsilon_1)Q\right)\delta_{n',n}\right.$$

$$\left.-(\epsilon_2\, Q'-\epsilon_1\, P'Q/P)(\delta_{n',n+1}+\delta_{n',n-1})\right]A'_{nm}$$

$$=\epsilon_1\sum_{n=-\infty}^{\infty}C'_{nm}(Q'-P'Q/P)\left[2\cosh\mu_1\delta_{n',n}-(\delta_{n',n+1}+\delta_{n',n-1})\right] \qquad (4.31)$$

Introducing further,

$$E_n^m=(\epsilon_2\, Q'-\epsilon_1\, P'Q/P)A'_{nm}$$

$$q_n^m=2\cosh\mu_1+\frac{(\epsilon_2-\epsilon_1)Q}{\epsilon_2\, Q'-\epsilon_1\, P'Q/P}$$

$$\lambda_n^m=\epsilon_1(Q'-P'Q/P)C'_{nm}, \qquad (4.32)$$

we obtain the following second-order difference equation for the coefficients E_n^m :

$$E_{n+1}^m-q_n^mE_n^m+E_{n-1}^m=\lambda_{n+1}^m-2\cosh\mu_1\lambda_n^m+\lambda_{n-1}^n \qquad (4.33)$$

The real and imaginary parts of this equation must be satisfied separately, leading to two difference equations which through eqs. (4.25) and (4.32), determine both the amplitude A_{nm} and the phase η'_{nm}. Eq (4.33) also arises in the problem of a dielectric torus in a uniform electric field (Love, 1972) and can be solved using

techniques of the Green function. Because it is rather technical, a sketch of the solution is given in the Appendix (3). As seen in the Appendix the solution involves an infinite sum of series of products. Therefore, it would be worthwhile to give some numerical results.

4.5 Comparism of the Solution of Poisson Equation for the Two Geometries

We have solved the Poisson equation for cylindrical and toroidal geometries analytically. The analytical solutions for the potential profiles obtained are quite cumbersome. The simulations of these geometries have been discussed in many works (Kuyucak S.et.al.,1998,Shung S-H.et.al.2002) . We hereby present numerically the graphical presentation of the potentials for cylindrical and toroidal geometries. See Fig (4.2)

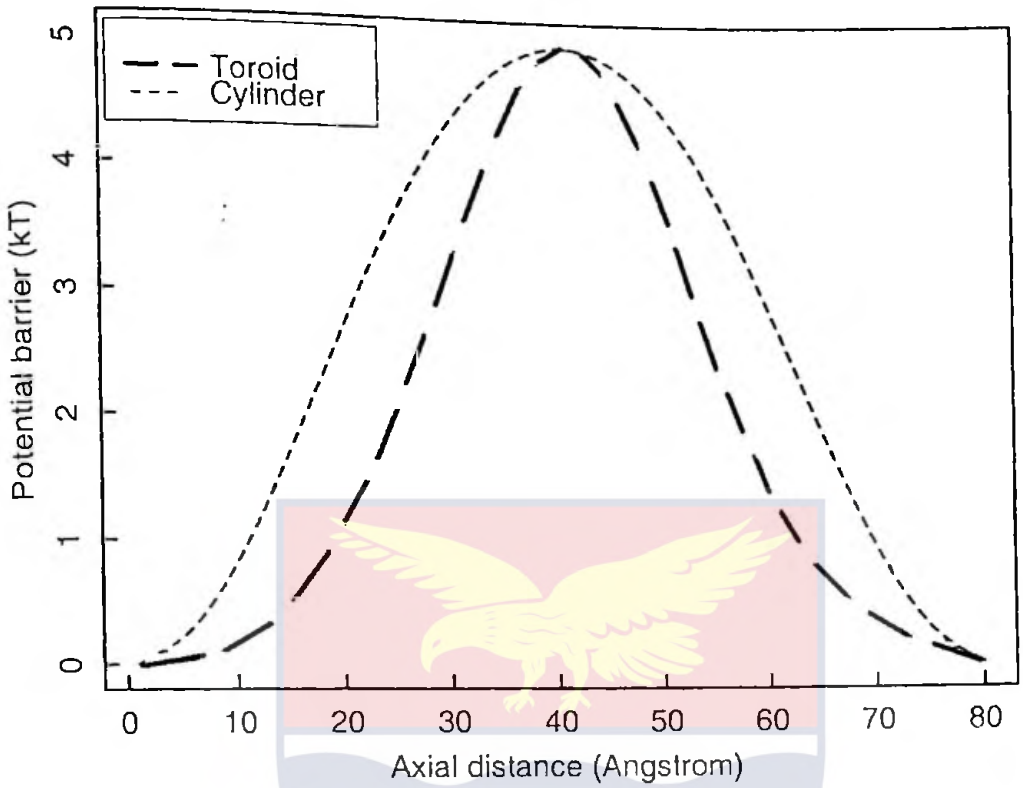

Figure 4.2 Potential profiles for the two geometrical approximations to ACh receptor channel.

In Fig (4.1a) it is assumed that flux is zero, or the walls and the potential ϕ is zero at both ends (Aidoo.,2001).We noted that channel geometry has substantial effect on the magnitude and distribution of the electrostatic potential. We, further noted the following

1. The maximum potential barrier for the two channel geometries occurs at the midsection of the channel. For the cylindrical geometry, the potential increases from zero very rapidly with axial distance than the toroidal geometry.

2. The potential encountered in the cylindrical channel geometry has about the same maximum as the toroidal channel (~ 4.8 KT). Considering the speed of a sodium ion in the ACh channel (about $40ms^{-1}$) it appears the estimate of the potential barrier from the cylinder and toroid are quite high, since the ion must overcome the potential barrier before traversing the channel.

4.6 Merits and Demerits of the Poisson Equation Model

The Poisson equation used here is based on classical electrostatic theory. This theory considers water to be a continuum and used the mean field approximation, which assumes that the potential can be determined from a continuous distribution of mobile charges. In addition, the size of the system under consideration must be small, that is less than the Debye length $(\sim 5.3A^{\circ})$ as it is with the case of the ACh membrane channel (Hille, 1992). This makes the Poisson equation more appropriate for the calculation of the potential profile in the ACh channel than, for example, the Eyring rate theory or the Poisson-Boltzmann equation. Another advantage of this approach is its computational efficiency. Unlike the molecular dynamics approach, for example, the model here leads to a considerable increase in computational efficiency, since only one linear partial differential equation is solved. The molecular dynamic approach, on the other hand, follows the laws of classical mechanics and relies on integrals of equations of motion of the interacting particles in a dynamical system.

CHAPTER FIVE

BIOLOGICAL IMPLICATIONS AND OUTLOOK

We have obtained a realistic cylindrical and toroidal channel geometries from the three dimensional oblate . This enabled us to calculate the electrostatic potential in the channel via the Poisson equation. Based on our electrostatic calculations, we were able to deduce that an ion permeating the ACh channel must overcome an energy barrier, which is higher in the absence of mobile charges than when mobile charges are present. We infer from our results that the potential barrier arises, possibly, due to surface charges. The nature of the potential barrier is such that no potential well is created within the channel, hence sodium or potassium ions cannot be trapped there, except when the channel closes momentarily. Once they are drawn into the channel, they must be ejected at the opposite end.

The ACh channel is endowed with many structural features. Our model and the electrostatic calculations carried out in the channel geometry could help in the understanding of some of the structural features of the ACh channel in particular, and similar ion channels in general. Features such as ion selectivity, which makes the channel permeable to sodium, potassium and calcium ions, but impermeable to chloride ions, for example, are determined by the electrostatic potential profile of the channel. These important ions diffuse across the ACh receptor channel following the electrochemical gradient, the

electrostatic component of which our model provides the means to evaluate accurately.

The model has profound biological implications. As electric potential changes are not only involved in many cellular processes, but are also responsible for the coding of information in the nervous system. First, the flow of ions through the ACh channel and other similar membrane channels is fundamental to all electrical phenomena in neurons. Knowledge of the electrostatic potentials in the channel assists in building up a theoretical framework that can be relied upon to explain different sets of data pertaining to the channel.

It has been stated in chapter one that signal communications in the nervous system depend greatly on membrane potentials. Indeed the neurotransmitter, ACh, and changes in membrane potentials are communication signals, and the potentials and ACh are the languages by which information is relayed in the nervous system. Our model has the potential of assuring a better understanding of this all-important physiological function, subsequent to understanding depolarization, which follows the inflow of ions into the channel.

Our model could be applied to gain a better understanding of muscle movement from the theoretical standpoint. The contraction of muscle fibers is initiated by an action potential which results from the flow of ions into the channel, so that the threshold value of the membrane potential is exceeded. A better insight into how this phenomenon operates could be gained by relying on

our channel geometry and for evaluating the membrane potentials that trigger the inflow of ion.

Again, our model could be applied beyond the direct biological evidence. It could also be utilized for the prediction of the dynamic behavior of ions in the ACh channel in particular, and similar ion channels in general, with a reliable degree of accuracy. Using the model geometry and the subsequently calculated electric potential profiles, it is possible to determine, or at least predict, ACh channel properties, which might be difficult or impossible altogether to observe by other means. For example, it is possible to describe solution phenomena in the ACh channel at microscopic level in terms of reaction field energy. The field can easily be computed from the electrostatic potential.

This work could assist in obtaining answers to a number of interesting questions pertaining to membrane channel in general, such as the effects of residue charges on ion concentration and other interesting biological phenomena that are facilitated by the ACh channel. In addition, by placing dipoles at the protein boundary of the constricted section of the channel, studies on reduction of the potential barrier could be done. Such a study could be extended to gain a better understanding of the selectivity property of the ACh channel.

With the availability of more realistic channel geometry, the study could be extended in various directions. For example, the steady-state could be studied more comprehensively when this work is extended to include the

concentration of sodium, potassium and chloride ions in the presence of the channel potential.

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APPENDIX 1

The cylinder is represented by the parametric equation with parameters (r, ϑ, z) as

$$\begin{cases} x = r\cos\theta \\ y = r\sin\theta \\ z = z \end{cases}$$

The Laplace equation in this domain is given by:

$$\nabla^2\phi = \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial\psi}{\partial r}\right) + \frac{1}{r^2}\frac{\partial^2\psi}{\partial\phi^2} + \frac{\partial^2\psi}{\partial z^2} = 0 \quad (1)$$

The solution of (1) can be obtained by the method of separation of the variables.

$$\psi = \phi(\phi)R(r)Z(z) \quad (2)$$

Putting (2) into (1) equation (1) is broken into

$$\frac{d^2\phi}{d\phi^2} + m^2\phi = 0 \quad (3)$$

$$\frac{1}{r}\frac{d}{dr}\left(r\frac{dR}{dr}\right) + \left(k^2 - \frac{m^2}{r^2}\right)R = 0 \quad (4)$$

$$\frac{d^2z}{dz^2} - k^2 z = 0 \quad (5)$$

The solutions of (3) –(5) given as

$$\phi = A\cos m\phi + B\sin m\phi \quad (6)$$

$$Z = \frac{\sinh k(l-z)}{\sinh kl} \quad (7)$$

$$R = c_1 J_m(kr) + c_2 J_m(kr) \quad (8)$$

Since the potential in the cylinder is obviously a periodic function of angle ϕ with the period 2π, the constant m must be an integer.

Furthermore, the constant c_2 must be equal to zero because otherwise the potential would be great on the axis of the cylinder, which, of cause, is impossible.

With the boundary condition

$$\psi_0(r\phi z)\big|_{r=0} = 0 \tag{9}$$

$$J_m(ka) = 0 \tag{10}$$

It follows from this that k has an infinite set of values, defined by the formula

$$k_{m_i} = \frac{\mu_{m_i}}{a}(i = 1,2,3\cdots; \qquad m = 0,1,2,\ldots) \tag{11}$$

where μ_{m_i}, μ_{m_i},... are the positive roots of the equation (10)

To obtain the solution of the equation (1) which also satisfies the boundary conditions

$$\psi(r\phi z)_{z=0} = \psi_0(r\phi)$$

we form the series

$$\psi(r\phi z) = \sum_{m=0}^{\infty}\sum_{i=1}^{\infty}\left[A_{m_i}\cos m\phi + B_{m_i}\sin m\phi\right]$$

$$J_m\left(\mu_{m_i}\frac{r}{a}\right)\frac{\sinh k_{m_i}(l-z)}{\sinh k_{m_i} l} \tag{12}$$

and require that

$$\psi(r\phi 0) = \sum_{m=0}^{\infty}\sum_{i=1}^{\infty}\left[A_{mi}\cos m\phi + B_{mi}\sin m\phi\right] +$$

$$J_m\left(\mu_{m_i}\frac{r}{a}\right) = \psi_o(r\phi) \tag{13}$$

to find the coefficients A_{m_i} and B_{m_i} we expand $\psi_0(r\phi)$ in the sine and cosine series over the interval $(0, 2\pi)$, i.e.

$$\psi_0(r\phi) = \sum_{m=0}^{\infty}\left[f_n(r)\cos m\phi + f_n^*(r)\sin m\phi\right] \tag{14}$$

where

$$f_0(r) = \frac{1}{2\pi}\int_0^{2\pi}\psi_0(r\theta)d\theta \tag{15}$$

$$f_n(r) = \frac{1}{\pi}\int_0^{2\pi}\psi_0(r\theta)\cos m\theta d\theta \tag{16}$$

$$f_n^*(r) = \frac{1}{\pi}\int_0^{2\pi}\psi_0(r\theta)\sin m\theta d\theta \tag{17}$$

Inserting (15) –(17) into (14)

$$\psi_0(r\phi) = \frac{1}{2\pi}\int_0^{2\pi}\psi_0(r\theta)d\theta + \sum_{m=1}^{\infty}\frac{1}{\pi}\int_0^{2\pi}\psi_0(r\theta)\cos m\theta d\theta$$

$$\cos m\phi + \sum_{m=1}^{\infty}\frac{1}{\pi}\int_0^{2\pi}\psi_0(r\theta)\sin m\theta d\theta \sin m\phi \tag{18}$$

Inserting (18) into (13) and comparing the coefficients

$$\frac{1}{2\pi}\int_0^{2\pi}\psi_0(r\theta)d\theta = \sum_{i=0}^{\infty}A_0, J_0\left(k_{0_i}r\right) \tag{19}$$

$$\frac{1}{\pi}\int_0^{2\pi}\psi_0(r\theta)\cos m\theta d\theta = \sum_{i=1}^{\infty}A_{m_i}, J_m\left(k_{m_i}r\right) \tag{20}$$

$$\frac{1}{\pi}\int_0^{2\pi}\psi_0(r\theta)\sin m\theta d\theta = \sum_{i=1}^{\infty}B_{m_i},\ J_m\left(k_{m_i}r\right) \tag{21}$$

Multiplying both sides of (1 9) by $J_0(k_{oj}, u)$ and integrate over o to a

$$\frac{1}{2\pi}\int_0^{2\pi}\psi_0(r\theta)d\theta\int_0^a uJ_0(k_{0j}u)du =$$

$$\sum_{i=1}^{\infty}A_{m_i}\int_0^a uJ_0(k_{oj},u)J_0(k_{oi},r)dr \qquad (22)$$

$$r = u \qquad \text{and} \qquad i = j$$

We obtain

$$\frac{1}{2\pi}\int_0^{2\pi}\psi_0(u,\theta)d\theta\int_0^a uJ_0(k_{0i},u)du = A_{0i}\frac{1}{2}a^2J_1^2(k_{0i}) \qquad (23)$$

$$A_{oi} = \frac{1}{\pi a^2 J_i^2(k_{oi})}\int_0^{2\pi}\psi_0(u\theta)d\theta\int_0^a J_0(k_{0i}u)du \qquad (24)$$

Similarly

$$A_{m_i} = \frac{2}{\pi a^2 J_{m+1}^2(k_{m_i})}\int_0^{2\pi}\cos m\theta d\theta\int_0^a u\psi_0(u\theta)J_m(k_{m_i}u)du \qquad (25)$$

$$B_{m_i} = \frac{2}{\pi a^2 J_{m+1}^2(k_{m_i})}\int_0^{2\pi}\sin m\theta d\theta\int_0^a u\psi_0(u\theta)J_m(k_{m_i}u)du \qquad (26)$$

Inserting (24 –26) into (12) we obtain

$$\psi(r\phi z) = \sum_{m=0}^{\infty}\sum_{n=1}^{\infty}\left\{\frac{\in}{\pi a^2 J_{m+1}^2(k_{m_i})}\right.$$

$$\left[\int_0^{2\pi}\cos m\theta\cos m\phi d\theta\int_0^a u\psi_0(u\theta)J_m(k_{m_i})du\times\right.$$

$$\left.\left.\int_0^{2\pi}\sin m\theta\sin m\phi d\theta\int_0^a u\psi_0(u\theta)J_m(k_{m_i}u)du\right]\times J_m(k_{m_i},r)\frac{\sinh k_{m_i}(l-z)}{\sinh k_{m_i}l}\right.$$

$$\psi(r\phi z)=\sum_{m=n}^{\infty}\sum_{n=1}^{\infty}\left[\frac{\in}{\pi a^2 J^2_{m+1}(k_{m_i})}\int_0^{2\pi} m(\phi-\theta)d\theta\right.$$

$$\left.\int_0^a u\psi_0(u,\theta)J_m(k_{m_i},u)du\right\}\frac{\sinh k_{m_i}(l-z)}{k_{mi}l}J_m(k_{ni}r)$$

APPENDIX 2

$$\nabla^2\psi = -4\pi p \tag{1}$$

Let seek the solution ψ as

$$\psi = \sum_{m,n,s} A_{mns}\cos[m(\phi-\phi_o)]\sin\frac{\pi nz}{l}J_m\frac{\pi\beta_{ns}r}{a}\Big) \tag{2}$$

which goes to zero at $z=0,\ z=l\ r=a$ the boundaries of the cylinder

Differentiating example (2) twice with respect to z and r we obtain $\nabla^2\psi$ as

$$\nabla^2\psi = \pi^2\sum_{m,n,s} A_{m,n,s}\left[\left(\frac{n}{l}\right)^2+\left(\frac{\beta_{ns}}{a}\right)^2\right]\times \cos[m(\phi-\phi_o)]\sin\left(\frac{\pi nz}{l}\right)j_m\left(\frac{\pi\beta_{ns}r}{a}\right) \tag{3}$$

Inserting Equation (3) into (1) we obtain

$$\pi^2\sum_{m,n,s} A_{mns}\left[\left(\frac{n}{l}\right)^2+\left(\frac{\beta_{ns}}{a}\right)^2\right]\cos[m(\phi-\phi_o)]\sin\left(\frac{\pi nz}{a}\right)J_m\left(\frac{\pi\beta_{ns}r}{a}\right)$$

$$= 4\pi p \tag{4}$$

now we seek p also as

$$p(r,\phi,z) = \sum_{mus}\beta_{mns}\cos[(\phi-\phi_o)]\sin\left(\frac{\pi nz}{l}\right)J_m\left(\frac{\pi\beta_{ns}r}{a}\right) \tag{5}$$

There equation (4) because

$$\sum_{mns}\left[\left(\pi^2 A_{mns}\left(\frac{n}{l}\right)^2\right]-4\pi\beta_{mns}\right)\cos[m(\phi-\phi_o)] \sin\left(\frac{\pi nz}{l}\right).J_m\left(\frac{\pi\beta_{mns}}{a}\right)=0 \tag{6}$$

Since $\cos[m(\phi-\phi_o)]\sin\left(\frac{\pi nz}{l}\right)J_m\left(\frac{\pi\beta_{ms}r}{a}\right)$

Then

$$\pi^2 A_{mns}\left[\left(\frac{n}{l}\right)^2+\left(\frac{\beta_{ms}}{a}\right)^2\right]-4\pi\beta_{mns}=0 \tag{7}$$

Hence

$$A_{mns}=\frac{4}{\pi}\left[\frac{\beta_{mns}}{\left(\frac{n}{l}\right)^2+\left(\frac{\beta_{mns}}{a}\right)^2}\right] \tag{8}$$

Therefore

$$\psi=\sum_{mns}\frac{4}{\pi}\left[\frac{\beta_{mns}}{\left(\frac{n}{l}\right)^2+\left(\frac{\beta_{mns}}{a}\right)^2}\right].\cos[m(\phi-\phi_o)]\sin\left(\frac{\pi nz}{l}\right).$$

$$J_m\left(\frac{\pi\beta_{mis}r}{a}\right)$$

Now we are suppose to find β_{mns} Going Back to equation (5)

$$p(r,\phi,z)=\sum_{mns}\beta_{mns}\cos[m(\phi-\phi_o)]\sin\left(\frac{\pi nz}{l}\right)J_m\left(\frac{\pi\beta_{mns}r}{a}\right)$$

Multiplying both sides of this equation by one of the eigenfunctions and integrating over the volume of the cylinder

$$\int_0^a rdr\int_0^{2\pi}d\phi\int_0^e dz\sin\frac{\pi nz}{l}J_m\left(\frac{\pi\beta_{mns}r}{a}\right)p(r\phi z)=$$

$$=\sum_{mns}\beta_{mns}\int_0^{2\pi}\cos[m(\phi-\phi_o)]d\phi\int_0^l\sin\pi\frac{nz}{l}\sin\frac{\pi nz}{l}dz\times \tag{10}$$

$$\int_0^a r J_{m'}\left(\frac{\pi\beta_{m's'}r}{a}\right) J_m\left(\frac{\pi\beta_{ms}r}{a}\right) dr \qquad (11)$$

From the R. H. S.

$$\int_0^{2\pi} \cos[m(\phi-\phi_o)]d\phi = \pi$$

$$\int_0^l \sin\frac{\pi n'z}{l}.\sin\frac{\pi nz}{l}\,dz = l \qquad (12)$$

$$n' = n$$

$$\int_0^a r \quad J_m\left(\frac{\pi\beta_{m's'}r}{a}\right) J_m\left(\frac{\pi\beta_{ms}r}{a}\right) dr =$$

$$= \frac{1}{2}a^2\left[J_{m+1}(\pi\beta_{ms})\right]^2$$

$$m' = m$$

$$s' = s$$

Therefore in the summation we are left with only $\beta_{mns}\pi l\frac{a^2}{2}\left[J_{m+1}(\pi\beta_{ms})\right]^2$ (13)

Hence Equation (10) becomes

$$\beta_{mns} = \frac{2}{\pi l a^2\left[J_{m+1}(\pi\beta_{ms})\right]^2}\int_0^a r_0 dr_0 \int_0^{2\pi} d\phi_0 \times$$

$$\int_0^l dz_0 \cos[m(\phi-\phi)]\sin\frac{\pi nz_0}{l} J_{m'}\left(\frac{\pi\beta_{ms}r_0}{a}\right).$$

$$p(r_o\phi_o z_o) \qquad (14)$$

Substituting Equation (14) into equation (9) we obtain

$$\psi(r,\phi,z)=\int_{o}^{r} r_o dr_o \int_{0}^{2\pi} d\phi_0 \int_{o}^{a} dz_o G(r\phi z|r_o\phi_o z_o)p(r_o\phi_o z_o) \quad (15)$$

where

$$G(r\phi z|r_o\phi_o z_c)=\sum_{mns}\frac{8l\left(\pi^2 la^2\right)\cos[m(\phi-\phi_o)]}{\left[\left(\frac{n}{l}\right)^2+\left(\frac{\beta_{ms}}{a}\right)^2\right]J_{m+1}(\pi\beta_{mn})}^2 \cdot$$

$$\sin\left(\frac{\pi zn}{l}\right)\sin\left(\frac{\pi nz}{l}\right).J_m\left(\frac{\pi\beta_{ms}r}{a}\right).J_m\left(\frac{\pi\beta_{ms}r_o}{a}\right)$$

The field inside the cylinder containing a uniform distribution of charge of unit density i.e. $p(r_o\phi_o z_o)=1$ is obtained by integrating equation (15) and this gives

$$\psi=\sum_{n,s}\frac{\left[32|\pi^3\beta_{os}(2n+1)\right]}{J_1\left(\pi\beta_{os}\left[(2n+1)/l\right]^2+\left(\beta_{os}/a\right)^2\right)}\sin\left[\frac{\pi z}{l}(2n+1)\right].$$

$$J_o\left[\frac{\pi\beta_{os}r}{a}\right]$$

APPENDIX 3

Here we sketch the solution of the second order difference equation (Eq 20, chapter 3) For convenience, we will suppress the superscript m, but the same equation, with different coefficients λ_n^m has to be solved for each values of m, The Green function corresponding to eq (4.20) in chapter 4 satisfies (See Love, 1972)

$$G_{n+1,N} - q_n G_{n,N} + G_{n,-1,N} = \delta_{n,N+1} - 2\cosh\mu_1 \delta_{n,N} + \delta_{n,N-1} \qquad (1)$$

for each values of N. Here $\delta_{n,N}$ denotes Kronecker delta. Solutions of Eq.(4.20) are then given by.

$$E_n = \sum_{N=-\infty}^{\infty} G_{n,N}\lambda_N \qquad (2)$$

as can be verified by substituting Eq.(2) into Eq. (20) and using Eq. (1) Construction of the Green function in Eq.(1) is conceptually similar to the familiar cases in electrostatics. One first finds the solutions of the homogeneous equation.

$$G_{n+1,N} - q_n G_{n,N} + G_{n-1,\,N} = 0 \qquad (3)$$

and then implements the "boundary conditions" implied in Eq.(1). The two independent solutions of Eq. (3) can be found from a study of its asymptotic form as $|n| \to \infty$. In that limit, $q \to 2\cosh\mu_1$. And the ratios $G_{n+1,N}/G_{n,N}$ for the solution tend to $\exp(\pm\mu_1)$. The solution Eq. (3) with the correct asymptotic are given in terms of the continued fraction as (see, for details, Milne-Thompson, 1960)

$$\frac{G_{n+1,N}}{G_{n,N}} = \cfrac{1}{1} \equiv \alpha_{n+1}$$
$$q_{n+1} - \cfrac{1}{}$$
$$q_{n+2} - \cfrac{1}{}$$
$$q_{n+3} - \cdots \tag{4}$$

$$\frac{G_{n-1,N}}{G_{n,N}} = \cfrac{1}{1} \equiv \beta_{n+1}$$
$$q_{n-1} - \cfrac{1}{} \equiv \alpha_{n+1}$$
$$q_{n-2} - \cfrac{1}{}$$
$$q_{n-3} - \cdots$$

Eq. (4) can be written as recursion relations among α_n and β_n:

$$\alpha_n = \frac{1}{q_n - \alpha_{n+1}}, \quad \beta_n = \frac{1}{q_n - \beta_{n-1}}. \tag{5}$$

Which provided a simple method for their calculation by iteration. From the symmetry properties of $P^m_{n-1/2}$, $Q^m_{n-1/2}$ and their derivatives (they remain invariant under $n \to -n$), it follows that $q_{-n} = q_n$ in Eq. 19. Using this fact in Eq. (5), it is seen that $\alpha_n = \beta_{-n}$, and therefore only one set of coefficients needs to be calculated. Rewriting Eq. (4) as

$$\begin{aligned} G_{n+1,N} &= \alpha_{n+1} G_{n,N}; & n \geq N+1 \\ G_{n-1,N} &= \beta_{n-1} G_{n,N}, & n \leq N\text{-}1 \end{aligned} \tag{6}$$

$G_{n,N}$ can be determined from Eq.(6) recursively. Once $G_{N+1,N}$ and $G_{N-1,N}$ are specified. To calculate these two quantities, we use the "boundary conditions" on Eq.(1) at $n = N-1, N, N+1,$ which gives the following equation :

$$(\beta_{N-2} - q_{N-1})G_{N-1,N} = 1$$

$$G_{N-1,N} - q_N G_{N,N} = -2\cosh\mu_1$$

$$G_{N,N} + (\alpha_{N+2} - q_{N+1})G_{N+1,N} = 1 \qquad (7)$$

where we have substituted $G_{N-2,N} = \beta_{N-2}G_{N-1,N}$ and $G_{N+2,N} = \alpha_{N+2}G_{N+1,N}$ from Eq.(6). These equations can be further simplified by using $\beta_{N-2} - q_{N-1} = -1/\beta_{N-1}$ and $\alpha_{N+2} - q_{N+1} = -1/\alpha_{N+1}$, which follow from Eq. (6). Solution of the set of linear equations in Eq . (7) yields.

$$G_{N-1,N} = \frac{(2\cosh\mu_1 - q_N)\beta_{N-1}}{q_N - \alpha_{N-1} - \beta_{N-1}}$$

$$G_{N,N} = \frac{(2\cosh\mu_1 - \alpha_{N+1} - \beta_{N-1})}{q_N - \alpha_{N+1} - \beta_{N-1}}$$

$$G_{N+1,N} = \frac{(2\cosh\mu_1 - q_N)\alpha_{N+1}}{q_N - \alpha_{N+1} - \beta_{N-1}} \qquad (8)$$

Substituting Eqs. (6) and (8) in Eq.(2), we finally obtain for the coefficients E_n,

$$E_n = \sum_{N=-\infty}^{\infty} \frac{\lambda_N}{(q_N - \alpha_{N+1} - \beta_{N-i})} \cdot$$

$$\{(2\cosh\mu_1 - \alpha_{N+1} - \beta_{N-1})\delta_{n,N} + 2\cosh\mu_1 - q_N\}$$

$$\left[\theta(n-N)\prod_{k=N+1}\alpha_k + \theta(N-n)\prod_{k=n}^{N-1}\beta_k\right] \qquad (9)$$

where $\theta(x)$ is the step function i.e $\theta(x)=1$ if $x>0$, and 0 otherwise.

Appendix 4

Application of Curvilinear coordinate

A coordinate system is said to be specified in space if every point P is associated with a triple of numbers q_1, q_2, q_3, distinct triples corresponding to distinct points in space. The numbers q_1, q_2, q_3 are called the coordinates (or curvilinear coordinates) of the point $P = P(q_1, q_2, q_3)$.

Let $p(q_1, q_2, q_3)$ be an arbitrary point in space, $P_1(q_1 + \Delta q_1, q_2, q_3)$ a point lying on the q_1-line of the point P, and let $|PP_1|$ be the length of the arc PP_1. Then the number

$$L_1 = \lim_{\Delta q_1 \to 0} \frac{|\breve{P}P_1|}{\Delta q_1}.$$

is called Lame's coefficient of the coordinate q_1 at the point P. (L_2 and L_3 of the coordinates q_2 and q_3 are defined in a similar manner).

If the point $P(x, y, z)$ has the curvilinear coordinate $q_1 = q_1(x, y, z)$, $q_2 = q_2(x, y, z)$, $q_3 = q_3(x, y, z)$, then the differentials of the radius vectors dr_{qv} of the coordinate lines and the differentials of their arcs dr_{qv} are determined as

$$dr_{qv} = i\frac{\partial x}{\partial q_v}dq_v + j\frac{\partial y}{\partial q_v}dq_v + k\frac{\partial z}{\partial q_v}dq_v = L_v e q_v \qquad (1)$$

$$ds_{qv} = \sqrt{\left(\frac{\partial x}{\partial q_v}\right)^2 + \left(\frac{\partial y}{\partial q_v}\right)^2 + \left(\frac{\partial z}{\partial q_v}\right)^2}\, dq_v = L_v e_{q_v} \qquad (2)$$

$(v = 1, 2, 3)$, where L_v are Lame's coefficients .

In order to obtain an expression for the Laplace operator, we can write the expression for the divergence of an arbitrary vector a, as

$$div\, a = \frac{1}{L_1 L_2 L_3}\left(\frac{\partial}{\partial q_1}\left(L_2 L_3 a_{q_1}\right)+\frac{\partial}{\partial q_2}\left(L_1, L_3 a_{q_2}\right)+\frac{\partial}{\partial q_3}\left(L_1 L_2 a_{q_3}\right)\right) \quad (3)$$

here $a = a_{q_1} e_{q_1} + a_{q_2} e_{q_2} + a_{q_3} e_{q_3}$

The gradient of the scalar filed is also given

$$\text{grad}\, u = \frac{1}{L_1}\frac{\partial u}{\partial q_1} e_{q_1} + \frac{1}{L_2}\frac{\partial u}{\partial q_2} e_{q_2} + \frac{1}{L_3}\frac{\partial u}{\partial q_3} e_{q_3} \quad (4)$$

We their obtain the Laplace operator as div grad u which is

$$\Delta u = \nabla^2 u = \frac{1}{L_1 L_2 L_3}\left(\frac{\partial}{\partial q_1}\left(\frac{L_2 L_3}{L_1}\frac{\partial u}{\partial q_1}\right)+\frac{\partial}{\partial q_2}\left(\frac{L_1 L_3}{L_2}\frac{\partial u}{\partial q_2}\right)+\frac{\partial}{\partial q_3}\left(\frac{L_1 L_2}{L_3}\frac{\partial u}{\partial q_3}\right)\right) \quad (5)$$

The following coordinate systems are commonly used.

(i) Cylindrical coordinate systems

(1) In this system the distance r from the point P to the z-xis is taken for $q_1 : q_1 = r(0 \le r < \infty)$, $q_2 = r$ is an angle formed by the projection of the radius vector 0P pm the xy-plane with the positive direction of the x-axis $(0 \le \varphi < 2\pi)$ $q_3 = z$ being the z-coordinate of the points P. Cylindrical coordinate are related with rectangular Cartesian coordinates through the following set of equations

$$\begin{aligned} x &= r\cos\varphi \\ y &= r\sin\varphi \\ z &= z \end{aligned} \quad (6)$$

Here $L_1 = L_3 = 1, \quad L_2 = r$

Hence, in cylindrical coordinates, r, φ, z

$$\Delta = \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial}{\partial r}\right)+\frac{1}{r^2}\frac{\partial^2}{\partial \varphi^2}+\frac{\partial}{\partial z^2} \quad (7)$$

(iii) Spherical coordinate system.

In this system $q_1 = r$ is the length of the radius vector of the point $P(0 \le r < \infty)$, $q_2 = \theta$ is the angle between the positive direction of the $z-$axis and the radius vector OP of the point $P(0 \le \theta \le \pi)$, q_3 being the angle between the positive

direction of the x-axis and the projection of the radius vector OP on the xy-plane $(0 \le \varphi < 2\pi)$.Again the relation to the Cartesion coordinates are given as

$$\begin{aligned} x &= r\sin\theta\cos\varphi \\ y &= r\sin\theta\sin\varphi \\ z &= r\cos\theta \end{aligned} \tag{8}$$

$L_1 = 1, \quad L_2 = r,$ and $L_3 = r\sin\theta$. Hence from eq(5) we obtain

$$\nabla = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial}{\partial r}\right) + \frac{1}{r^2\sin\theta}\frac{\partial}{\partial\theta}\left(\sin\theta\frac{\partial}{\partial\theta}\right) + \frac{1}{r^2}\frac{1}{\sin^2\theta}\frac{\partial^2}{\partial\varphi^2} \tag{9}$$

(ii) Toroidal Coordinates: A point P anywhere in space can be defined by μ, η, ϕ. The coordinate μ describes a ring of circles. The radius of the circle decreases progressively, and its center moves in from ∞ to point L on the x axis as μ increases from 0 to ∞. For a given μ, η traces a circle of fixed radius as it goes from 0 to 2π. With $\eta = 0$ furthest from the $z-axis$, and $\eta = \pi$ nearest. The coordinate ϕ is the azimuthal angle about the z axis.

A point anywhere in space can be defined in Toroidal coordinate system as (η, μ, φ).

where μ ranges from O to ∞, η from O to 2π and Φ from 0 to 2π.

The toroidal coordinates are related to the Cartesian ones through the following set of equations

$$z = \frac{a\sin\eta}{\cosh\mu - \cos\eta}$$

$$x = \frac{a\sinh\cos\varphi}{\cosh\mu - \cos\eta}$$

$$y = \frac{a\sinh\mu\cos\varphi}{\cosh\mu - \cos\eta}$$

with respect to eq (2)

$$L_1 = L_2 = \frac{a}{\cosh\mu - \cos\eta} \qquad L_3 = \frac{a\sinh\mu}{\cosh\mu - \cos\eta} \tag{10}$$

and hence Laplace of ψ in given as

$$\nabla_\psi^2\psi = \frac{1}{L_1^3}\left[\frac{1}{\sinh\mu}\frac{\partial}{\partial\mu}\left(L_1\sinh\mu\frac{\partial\psi}{\partial\eta}\right)+\frac{\partial}{\partial\eta}\left(L_2\frac{\partial\psi}{\partial\eta}\right)+\frac{L_1}{\sinh^2\mu}\frac{\partial^2\psi}{\partial\psi^2}\right] \tag{11}$$

We again set

$$\psi = \sqrt{\cosh\mu}-\cos\eta\, F(\mu,\eta,\varphi) \tag{12}$$

and find that the Laplace equation reduces to

$$\frac{1}{\sinh\mu}\frac{\partial}{\partial\mu}\left(\sinh\mu\frac{\partial F}{\partial\mu}\right)+\frac{\partial^2 F}{\partial\mu^2}+\frac{1}{\sinh^2\mu}\frac{\partial^2 F}{\partial\phi^2}+\frac{1}{n}F=0 \tag{13}$$

The ϕ factor is $\cos(m\phi)$ or $\sin(m\phi)$ and since ϕ is a periodic coordinate, m is zero or a positive integer to ensure continuity. Coordinate η is also periodic, so that the η factor must also be $\cos(n\eta)$ or $\sin(n\eta)$ with n zero or an integer.

The solutions of Laplace's equation in toroidal coordinates are therefore given in terms of the series as

$$\psi = \sqrt{\cosh\mu-\cos\eta}\sum_{m=0}^{\infty}\sum_{n=0}^{\infty}\left[a_m\cos(m\phi)+b_m\sin(m\phi)\right]$$

$$\left[C_n\cos(n\eta)+d_n\sin(n\eta)\right]\left[A_{mn}P^m_{n-\frac{1}{2}}(\cosh\mu)+B_{mn}Q^m_{n-\frac{1}{2}}(\cosh\mu)\right]. \tag{14}$$

$$L_1 = L_2 = \frac{a}{\cosh\mu - \cos\eta} \qquad L_3 = \frac{a\sinh\mu}{\cosh\mu - \cos\eta} \tag{10}$$

and hence Laplace of ψ in given as

$$\nabla^2_\psi \psi = \frac{1}{L_1^3}\left[\frac{1}{\sinh\mu}\frac{\partial}{\partial\mu}\left(L_1\sinh\mu\frac{\partial\psi}{\partial\eta}\right)+\frac{\partial}{\partial\eta}\left(L_2\frac{\partial\psi}{\partial\eta}\right)+\frac{L_1}{\sinh^2\mu}\frac{\partial^2\psi}{\partial\psi^2}\right] \tag{11}$$

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$$\left[C_n\cos(n\eta)+d_n\sin(n\eta)\right]\left[A_{mn}P^m_{n-\frac{1}{2}}(\cosh\mu)+B_{mn}Q^m_{n-\frac{1}{2}}(\cosh\mu)\right]. \tag{14}$$