Dynamics and structure of polyelectrolyte complexes

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DYNAMICS AND STRUCTURE OF POLYELECTROLYTE COMPLEXES

A Dissertation Presented

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ABSTRACT

DYNAMICS AND STRUCTURE OF POLYEOLECTROLYTE COMPLEXES

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Interaction of charged macromolecules among themselves and with charged interfaces in salty aqueous medium is a common phenomenon prevalent in biology and synthetic systems. We have addressed several inter-related issues in this general context. First we present a theory of adsorption of polyelectrolytes on the interior and exterior surfaces of a charged spherical vesicle. We derive the critical adsorption condition and the density profile of the polymer in terms of various characteristics of the polymer, vesicle, and the solution, such as the length and charge density of polymer, the radius and charge of the vesicle, the salt concentration of the solution, and the dielectric constant of the solvent. We have used the Wentzel-Kramers-Brillouin (WKB) method to solve the equation for the probability distribution function of the chain. For the polyelectrolyte inside the vesicle, the competition between the loss of conformational entropy and the attractive electrostatic energy between the vesicle...
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For a vesicle, we have derived the free energy landscape of translocation through the pore by accounting for the energy penalty of bending and stretching the vesicle from due to deformation by pore. Using the Fokker-Planck formalism, we have calculated the average translocation time corresponding to the various free energy landscapes representing different parameter sets. We also discuss the dependencies of the average translocation time on the strength of the external force, vesicle size, bending and stretching moduli of the vesicle, and the radius and length of the pore. Finally, we formulate a theory of the effects of long-range interactions on surface tension and spontaneous curvature of proteinaceous shells based on the general Deryaguin-Landau-Verwey-Overbeek (DLVO) theory. We have derived the renormalized spontaneous curvature as a function of capsid’s inner and outer charge density and solution properties.
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CHAPTER 1
INTRODUCTION

A polyelectrolyte is a macromolecule where a large number of electrically charged repeat units, called monomers, are contiguously connected in a linear manner as sketched in Fig. 1.1. Here, every repeat unit is assumed to be negatively charged as an example of a polyanion. If all repeat units are positively charged, then the polyelectrolyte is called a polycation. Examples of polyelectrolytes include natural polymers such as single-stranded DNA (Fig. 1.2a) and double-stranded DNA (Fig. 1.2b) and synthetic polyelectrolytes such as poly(styrene sulfonate) (Fig. 1.2c).

The polyelectrolytes sketched in Fig. 1.1 and illustrated in Fig. 1.2 are not stable on their own due to the explosive amount of electrostatic repulsion among the various charged monomers.

These macromolecules exist only as their salts with small oppositely charged ions in their solid forms. Only when these polyelectrolyte salts are dissolved in a polar solvent such as water, the polyelectrolyte sketched in Fig. 1.1 can exist along with a certain number of oppositely charged ions, called counterions, just enough to balance the net charge of the polyelectrolyte so that the total system is electrically neutral. This stable condition corresponding to the maintenance of global electroneutrality is depicted in 1.3, where the counterions taken to be positively charged, are denoted in blue color. In addition, it is common to disperse a controllable amount of strong electrolytes such as table salt into the polyelectrolyte solution. The cations and an-
Figure 1.1: Schematics of the structure of a polyelectrolyte chain. In this figure, monomers are negatively charged.

Figure 1.2: Three of the more common polyelectrolytes: a) single-stranded DNA; b) double-stranded DNA *; c) chemical structure of poly (styrene sulfonate).

ions emerging from the full dissociation of the added salt, often referred to as simple electrolyte, are denoted in circled charges, in Fig.1.3.

*Fig. 1.2b: By Zephyris - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=15027555
An exact theoretical treatment of a polyelectrolyte chain still remains a challenge. The primary reasons for this challenge are threefold. First, even aqueous solutions of fully dissociated simple electrolytes, such as salty water in a pan, is difficult to theorize despite the famous theory of Debye and Hückel valid for infinitely dilute conditions. Second, the polymer backbone on which charges are covalently attached is itself topologically correlated through chain connectivity. Third, the long-ranged electrostatic repulsion among the various repeat units of the polymer is being modulated by chain connectivity and the electrostatic forces emanating from the translationally free counterions and dissociated electrolyte ions. In spite of the challenges presented by these issues, considerable progress has been made by polymer physicists to theoretically address polyelectrolyte solutions, as it is described briefly below and in the following chapters.

Although a proper theoretical description of a polyelectrolyte chain can be of great excitement for theorists, such systems on their own are of limited value in practical situations. What is of broad interest and impact to society is how such
polyelectrolytes interact with other macromolecular systems in aqueous media. As an example, consider the practice of gene therapy or fabrication of membranes for water purification by the phenomenon of coacervation. The essential steps in gene therapy involve packaging DNA of designed sequence into a vesicle or a virus-like vessel and then releasing the DNA out of the vesicle (shown in Fig. 1.4a-b). Alternatively, the DNA first complexes with another polyelectrolyte of opposite charge and later it ejects out of the complex by decomplexing (see in Fig. 1.4c).
The polyelectrolyte partners in Fig. 1.4c are of course oppositely charged. The complexity of the problem and the associated challenge in its theoretical treatment are to be contrasted with the formation of an ion-pair from one cation and one anion. Even in Fig. 1.4a, the theoretical treatment is challenging due to the frustration on the polyelectrolyte chain induced by the curvature and the opposite charge of the vesicle. In view of both the practical significance and the tremendous theoretical challenge, we have taken up (1) complexation of a polyelectrolyte inside an attractive spherical vesicle, (2) complexation of a polyelectrolyte outside an attractive spherical vesicle, and (3) complexation between two oppositely charged polyelectrolyte chains as the primary themes of my thesis (Fig. 1.5). The third theme also addresses the kinetics of approach of two oppositely charged polyelectrolyte chains.

Now, how is a polyelectrolyte chain modeled theoretically? Let us first consider only the chain connectivity without charges or intra-chain van der Waals interactions. Imagine a trajectory of $N$ steps of a random walker sketched in Fig. 1.6. This trajectory can be imagined to represent a conformation of a polymer chain without any intra-chain potential interactions. Such a mapping is called the Kuhn model of $N$ Kuhn steps, each of step length $\ell$, called the Kuhn length. All chemical details along
the backbone of the chain are parametrized in terms of the Kuhn length. Beyond the Kuhn length along the chain backbone, the tangent vectors along the backbone are uncorrelated.

It is well known that the probability $P_0(r, t; r_0(0))$ of finding a particle undergoing a random walk in three-dimensional space from the initial position $r_0$ at $t_i = 0$ to its final position, $r$, at time $t_f = t$ is given by

$$P_0(r, t; r_0(0)) = \left( \frac{1}{4\pi D t} \right)^{3/2} e^{-\frac{(r-r_0)^2}{4Dt}} \quad (1.1)$$

where the mean square displacement of the particle follows the law of diffusion,

$$\left\langle (r - r_0)^2 \right\rangle_0 = 6Dt \quad (1.2)$$

with $D$ being the diffusion coefficient and $t$ being proportional to the number of steps taken by the random walker.

Using Kuhn’s mapping between a collection of trajectories of a random walker and the various conformations of the Kuhn model chain, the probability distribution
function \( G_0(r, r'; N) \) of a Kuhn chain of \( N \) Kuhn segments with its ends at \( r \) and \( r' \) follows immediately, by analogy, from Eq. (1.1) as [3, 4]

\[
G_0(r, r'; N) = \left( \frac{3}{2\pi N\ell^2} \right)^{3/2} e^{-\frac{3(r-r')^2}{2N\ell^2}}
\]

(1.3)

Due to the Gaussian nature of this distribution function, the Kuhn chain is also referred to as the Gaussian chain. The mean square end-to-end distance of a Gaussian chain follows from Eq. (1.3) as

\[
\langle (r - r')^2 \rangle_0 = N\ell^2
\]

(1.4)

where the angular brackets denote the average over \( G_0 \) given by 1.3. An experimentally relevant measure of the polymer size is the radius of gyration \( R_g \), defined by

\[
R_g^2 = \frac{1}{(N + 1)} \sum_{i=0}^{N} \langle r_i^2 \rangle
\]

(1.5)

where \( r_i \) is the position of the \( i \)-th repeat unit (sometimes called bead) from the center of mass of the chain. Again, the angular brackets denote the average over \( G_0 \) given by Eq. (1.3).

For a Gaussian chain, it can be easily shown from Eqs. (1.3) and (1.4) that

\[
R_g^2 = \frac{N\ell^2}{6}
\]

(1.6)

It is of common practice for very good reasons, based on knowledge of critical phenomena and field theory of polymers, to define the size exponent \( \nu \) relating \( R_g \) and the number of Kuhn segments, \( N \), as
\[ R_g \approx N^\nu \] (1.7)

For Gaussian chains, it is readily obvious that

\[ \nu = \frac{1}{2} \] (1.8)

and referred to as the mean field exponent.

An alternate representation of \( G_0(r, r'; N) \) of Eq. (1.3) is its form as a path integral

\[
G_0 (r, r'; N) = \int_{r'}^r \mathcal{D} [r(s)] \exp \left\{ -\frac{3}{2\ell^2} \int_0^N ds \left( \frac{\partial r(s)}{\partial s} \right)^2 \right\}
\] (1.9)

where \( r(s) \) denotes the location of the arc length variable \( s \) \((0 \leq s \leq N)\) and the functional integral represents the sum over all possible configurations of the chain with the constraint of chain connectivity.

Yet another representation of \( G_0 \) is in its form of a differential equation,

\[
\left( \frac{\partial}{\partial N} - \frac{\ell^2}{6} \nabla_r^2 \right) G_0(r, r'; N) = \delta (r - r')
\] (1.10)

where \( G_0 \) is now treated as a Green function.

As already mentioned above, the Gaussian chain accounts for only chain connectivity. In reality, there are potential interactions among various Kuhn segments, both short-ranged and long-ranged. By writing a generic form for the potential interaction between two segments \( s \) and \( s' \) as
the probability distribution function for the chain of $N$ Kuhn segments to have the ends at $\mathbf{r}$ and $\mathbf{r}'$ is given as

\[ G_0 (\mathbf{r}, \mathbf{r}'; N) = \int_{\mathbf{r}'}^{\mathbf{r}} D [\mathbf{r}(s)] \exp \left\{ -\frac{3}{2\ell^2} \int_0^N ds \left( \frac{\partial \mathbf{r}(s)}{\partial s} \right)^2 - \int_0^N ds V_p [\mathbf{r}(s)] \right\} \]  \hspace{1cm} (1.11)

where

\[ V_p [\mathbf{r}(s)] = \frac{1}{2} \int_0^N ds' V [\mathbf{r}(s) - \mathbf{r}(s')] . \]  \hspace{1cm} (1.12)

As described in several textbooks on polymer physics [3], this path integral representation of $G$ can be equivalently written as

\[ \left( \frac{\partial}{\partial N} - \frac{\ell^2}{6} \nabla^2 + \beta V(\mathbf{r}(s)) \right) G_0 (\mathbf{r}, \mathbf{r}'; N) = \delta (\mathbf{r} - \mathbf{r}') \]  \hspace{1cm} (1.13)

It is obvious from Eqs. (1.11) and 1.12 that $V(\mathbf{r}(s))$ appearing in Eq. (1.13) depends on $G$ and hence a self-consistent procedure needs to be implemented in determining $G$ and in calculating the final result of $R_g$ and other properties of the non-Gaussian chain. We will describe several methods of accomplishing this goal in the following chapters. We must also mention that any effects due to chain stiffness is ignored and we consider only flexible chains with interactions.

Now, returning to the main focus of this thesis, namely complexation of a polyelectrolyte chain with a curved surface or another polyelectrolyte chain, let us denote the potential created by the surface or another chain on the position $\mathbf{r}(s)$ of the primary chain as $V_S[\mathbf{r}(s)]$. By including this effect, the probability distribution function of the chain becomes
\[
G (\mathbf{r}, \mathbf{r}'; N) = \int_{\mathbf{r}(0)=\mathbf{r}'}^{\mathbf{r}(N)=\mathbf{r}} \mathcal{D}[\mathbf{r}(s)] \exp \left\{ - \frac{3}{2\ell^2} \int_0^N ds \left( \frac{\partial \mathbf{r}(s)}{\partial s} \right)^2 - \frac{1}{k_B T} \int_0^N ds V_p[\mathbf{r}(s)] - \frac{1}{k_B T} \int_0^N ds V_s[\mathbf{r}(s)] \right\},
\]
so that
\[
\left[ \frac{\partial}{\partial N} - \frac{\ell^2}{6} \nabla_{\mathbf{r}}^2 + V_p(\mathbf{r}) + V_s(\mathbf{r}) \right] G (\mathbf{r}, \mathbf{r}'; N) = \delta (\mathbf{r} - \mathbf{r}') \delta(N).
\]

The solution of these equations for the prescribed intra-chain potentials (both short-ranged and long-ranged) and the electrostatic potentials between the polyelectrolyte chain and the charged vesicle, or another polyelectrolyte chain constitutes the major effort of my thesis. Once \(G\) is calculated, all experimentally relevant quantities such as the critical conditions for complexation, the segment density profile of the complexed polyelectrolyte chain can then be computed. Due to the structure of Eq. (1.15), it is obvious that the present classical problem can be mapped into the quantum problem of a particle in a box. Indeed, We have implemented several techniques of calculation of bound states and scattering states from the time-dependent Schrödinger equations, such as the variational and Wentzel-Kramers-Brillouin (WKB) [5–8] methods as described in the following chapters.

In the experiment ...

In addition to the above mentioned equilibrium aspects of polyelectrolyte complexation, it is of considerable interest to formulate a theory of kinetics of how a polyelectrolyte chain approaches another polyelectrolyte chain of opposite charge. For ions this is equivalent to a cation and an anion can approach towards each other and form a pair in an aqueous medium (Fig. 1.7).
Figure 1.7: a) complexation of two oppositely charged ions. b) complexation of two oppositely charged polyelectrolytes.

This interesting problem has been of immense theoretical interest in the past and several great scholars have contributed to this field. One way to approaching this problem is to write a continuity equation for one of the ions, keeping the center of mass of the other ion as the center of the reference frame and compute the flux of the first ion at the center, subjected to the Coulomb force between the ions. Now, the question is how to treat the approach of a topologically correlated polyelectrolyte chain to another polyelectrolyte chain which is also topologically correlated and there is a Coulomb potential between all segments of both chains (1.7b). This issue and our method is tackled at Chapter 3.

Furthermore, We have investigated potential means of measuring the elasticity of a vesicle by forcing it to undergo translation through a narrow pore by constructing a theory with the use of the Fokker-Planck formalism (see Fig. 1.8a). The details are presented in Chapter 4. Also, We have addressed the consequence of structure of the vesicle. Most of the vesicles are made of double layers, where hydrophilic ends of the constituent surfactant molecules of the vesicle are exposed to the outer and inner
Figure 1.8: a) translocation of a spherical vesicle through a pore. b) effect of DLVO interaction on spontaneous curvature and surface tension. †

interfaces of the vesicle. Inside the interior, the hydrophobic ends of the surfactant molecules are present. As a result, the vesicle is an intrinsically heterogeneous dielectric medium (see Fig. 1.8b). By implementing the techniques used to calculate the Casimir forces in finite-sized systems, we calculate the surface tension, bending modulus, and spontaneous curvature of the vesicle. This calculation, which is technically challenging, is described in Chapter 5.

†Fig. 1.8b is from Ref. [9]
CHAPTER 2

ADSORPTION AND ENCAPSULATION OF FLEXIBLE POLYELECTROLYTES IN CHARGED SPHERICAL VESICLES

2.1 Introduction

Packaging of charged macromolecules into vesicular carriers in aqueous media and their subsequent release into the exterior region are of common occurrence. The manifestation of this phenomenon in the context of biology and technological applications is well documented in the literature exhibiting very rich phenomenology [10, 11]. Yet, even the elementary aspects of the packing/unpacking of charged macromolecules by carriers are not fully understood, although some progress is being made in the study of viruses [9, 12–16]. The ubiquitous feature of this phenomenon is that both the macromolecular cargo and the vesicular interface are electrically charged. The interactions between the cargo and the oppositely charged vesicle arise primarily from the long-range electrostatic forces. Furthermore the macromolecular cargo itself is topologically correlated mediated by the electrostatic interactions among various segments of the molecule. In addition, the whole process occurs in aqueous electrolyte solutions with cargo-vesicle interaction being significantly modulated by changes in the electrolyte concentration. A full understanding of this packing-unpacking phenomenon continues to be a challenge due to the combined effects from the long-range electrostatic forces, topological connectivity of the macromolecules, confinement of cargo inside the vesicle, and adsorption of the cargo at the vesicle interface.

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In efforts to make progress towards a fundamental understanding of this packing-unpacking process and to ascertain the energetics of this process, we consider the initial and final states of the macromolecule in this process (Fig. 2.1): (1) The polymer is captured on exterior of the vesicle as an adsorbed chain, and (2) the polymer is adsorbed on the interior of the vesicle.

Naturally, there are several fundamental questions that arise regarding these two states. For the exterior state (Fig. 2.1a), identification of the critical condition of adsorption and the monomer density profile of the adsorbed polymer in terms of various experimental variables are of interest. The critical condition emerges as a compensation between attractive interaction favoring adsorption and loss of conformational entropy disfavoring adsorption. If the attraction between the polymer and the vesicle is weak, the adsorption would not occur at all due to the severe entropic penalty. For sufficiently strong attraction, adsorption would occur. It is therefore necessary to accurately evaluate the conformational entropy of a flexible polyelectrolyte chain that is partially adsorbed to a curved charged interface in order to obtain the adsorption criterion. For the interior state (Fig. 2.1b), if the attraction between the polymer and vesicle is sufficiently weak, the cargo will merely be confined inside the vesicle. For sufficiently strong attractive interaction, the polymer would coat the in-
terior wall of the vesicle. The adsorption criterion delineating these two limits in the interior is obtained by evaluating the conformational entropy of the polyelectrolyte chain under confinement inside an electrostatically interactive vesicle. In addition, due to confinement effects, an optimum radius of the vesicle may arise for coating the polyelectrolyte chain in the interior. The adsorption criteria, density profiles, and optimum vesicle radii are dictated by the various experimental variables.

The experimental variables pertinent to the process are the polymer charge number density $q$, polymer length $L$, vesicle surface charge number density $\sigma$, vesicle radius $R$, and the uniform electrolyte concentration $c_s$. The temperature $T$ and the presumed uniform dielectric constant $\epsilon$ of the medium are expressed in terms of the Bjerrum length $\ell_B = e^2/(4\pi\epsilon_0\epsilon k_B T)$, where $e$ is the electronic charge, $\epsilon_0$ is the permittivity of vacuum, and $k_B$ is the Boltzmann constant. The Bjerrum length sets the scale for the strength of the electrostatic interaction energy. The spatial range of the electrostatic interaction is captured roughly by the Debye length $\kappa^{-1}$ which is proportional to $1/\sqrt{c_s}$. The adsorption criteria and the density profiles for both the exterior and interior states and the optimum vesicle radii for the interior state are to be calculated in terms of the experimental parameters $q, L, \sigma, R, \ell_B$, and $\kappa$. Calculation of the free energy difference $\Delta F$ between the exterior and interior states of the polyelectrolyte chain would enable the estimation of energy costs for translocating the chain from the interior state to the exterior state, and their relative thermodynamic stabilities.

Adsorption of a polyelectrolyte chain onto a spherical charged surface from its exterior has attracted considerable effort based on theoretical approaches [17–35], computer simulations [36–49], and experiments [50–55] as nicely described in a recent review [20]. Planar and cylindrical interfaces for the exterior state and confinement of a polyelectrolyte chain inside a spherical cavity have also been investigated, although not as extensively as the exterior state for spherical cavities [18, 20, 24]. In general,
the conclusions deduced from these studies are inconclusive and various theoretical predictions appear to depend on the specifics of the model and the approximations used in the calculations. Since the primary focus of the present paper is in the context of adsorption onto spherical vesicles, we now briefly summarize the current status in this context only.

According to all previous theoretical works [22–35], starting from the pioneering work of Wiegel [21], the adsorption phase transition can be triggered by any of the experimental variables: surface charge number density $\sigma$, vesicle radius $R$, polymer charge number density $q$, temperature and dielectric constant appearing through the Bjerrum length $\ell_B$, salt concentration appearing through $\kappa$, and the polymer length $L$. For example, an increase in surface charge number density above a critical value $\sigma_c$ would result in adsorption when all other experimentally relevant quantities are held constant. Similarly lowering the temperature or decreasing the salt concentration would lead to adsorption. Almost all experiments reported so far in the literature [50–55] are conducted at a fixed room temperature and the critical condition for adsorption is determined experimentally by relating surface charge density and salt concentration. By considering adsorption of synthetic polyelectrolytes on micelle, proteins, and dendrimers, the empirically suggested critical condition is [20, 50–55]

$$|\sigma_c| \sim \kappa^a, \quad a \approx 1 - 1.4. \quad (2.1)$$

On the other hand, the various theoretical predictions [20] for the value of the exponent $a$ range from 6/5 to 3 for the experimental conditions pertinent to Eq. (2.1), namely $\kappa R >> 1$. In the other limit, $\kappa R << 1$, corresponding to the low salt limit, the range of $a$ predicted by theories [20] is from 1 to 3. However, this latter limit is not relevant to experimental situations establishing Eq. (2.1). Briefly, the models and assumptions behind the previous theoretical approaches are as follows.
The probability distribution function $G(r, r'; N)$ for a flexible polyelectrolyte chain of contour length $L = N\ell$ with its ends at $r$ and $r'$, in the proximity of a charged surface is given by the Edwards path integral [22] (for more details, see the description of Eq. (1.14)),

$$G(r, r'; N) = \int_{r(0)=r'}^{r(N)=r} \mathcal{D}[r(s)] \exp \left\{ -\frac{3}{2\ell^2} \int_0^N ds \left( \frac{\partial r(s)}{\partial s} \right)^2 - \frac{1}{k_B T} \int_0^N ds V_p[r(s)] - \frac{1}{k_B T} \int_0^N ds V_s[r(s)] \right\},$$

(2.2)

where $r(s)$ is the position vector of the arc length variable $s$ ($0 \leq s \leq L$), and $\ell$ is the Kuhn length. $V_p$ denotes the various inter-segment interactions of the chain acting on the segment at $r(s)$. $V_s$ is the electrostatic potential from the charged surface acting on the polymer segment at $r(s)$. The symbol $\int \mathcal{D}[r(s)]$ denotes the functional integration representing the sum over all possible chain configurations subjected to constraints from all intra-chain interactions and interaction with the surface. The path integral representation of Eq. (2.2) can be equivalently written as (see Eq. (1.15))

$$\left[ \frac{\partial}{\partial N} - \frac{\ell^2}{6} \nabla_r^2 + \frac{V_p[r]}{k_B T} + \frac{V_s[r]}{k_B T} \right] G(r, r'; N) = \delta(r - r')\delta(N).$$

(2.3)

By drawing an analogy with the time-dependent Schrödinger equation for a particle in a potential, the time-independent version is

$$G(r, r'; N) = \sum_m \psi_m(r)\psi_m^*(r') e^{-\lambda_m N},$$

(2.4)

with

$$\left[ -\frac{\ell^2}{6} \nabla_r^2 + \frac{V_p[r]}{k_B T} + \frac{V_s[r]}{k_B T} \right] \psi_m(r) = \lambda_m \psi_m(r).$$

(2.5)

For a chosen set of potentials $V_p$ and $V_s$, and appropriate boundary conditions, the eigenvalue problem of Eq. (2.5) is solved for $\psi_m(r)$ and $\lambda_m$, from which the probability distribution function $G(r, r'; N)$ is obtained from Eq. (2.4). The various
experimentally relevant features such as the adsorption criteria and density profiles of the adsorbed chain follow from \( G(r,r';N) \). Based on the quantum analogy with a particle in a potential, the adsorption criterion corresponds to the condition at which at least one bound state is allowed by Eq. (2.5). If the combined potential \((V_p + V_s)/k_B T\) is attractive and sufficiently strong, the polymer chain would adsorb corresponding to the occurrence of bound states. If the combined potential is weaker than a critical value, then only scattering states are allowed by Eq. (2.5) representing unadsorbed states of the polymer chain. Once the adsorption criterion is established, the density profile in the adsorbed state is calculated from the eigenfunctions \( \psi_m \) and eigenvalues \( \lambda_m \). Since the contour length of the polymer \( L = N\ell \) is usually very large, the leading term in Eq. (2.4) representing the ground state is often sufficient in the calculation of \( G(r,r';N) \).

The simplest situation of an infinitely thin and infinitely large planar charged interface somewhere in the middle of an electrolyte solution and an adsorbing Gaussian chain was initially treated by Wiegel [21]. For a uniform surface charge number density \( \sigma \) and linear polymer charge number density \( q \), the electrostatic interaction energy between the surface and a polymer segment at a distance \( z \) perpendicular to the interface is

\[
\frac{V_s(z)}{k_B T} = -2\pi|\sigma q|\frac{\ell B}{\kappa} e^{-\kappa z},
\]

(2.6)
based on the linearized Poisson-Boltzmann description. Ignoring the intra-chain interaction, namely by taking \( V_p = 0 \), Wiegel derived the exact adsorption criterion for this idealized model as [21]

\[
|\sigma_c| = \frac{\kappa^3\ell}{48\pi \ell_B |q| j_{0,1}^2} \sim \kappa^3,
\]

(2.7)

where \( j_{0,1} \approx 2.4048 \) is the first zero of the Bessel function \( J_0(x) \) for \( x > 0 \).

Since isolated flexible polyelectrolyte chains do not obey Gaussian chain statistics (where the radius of gyration \( R_g \sim \sqrt{N} \)), due to the electrostatic repulsion between
segments, Eq. (2.7) is not relevant to experimental situations. In view of this, one of the present authors [22] addressed the role of $V_p$ in Eqs. (2.3) and 2.5. Even in the absence of an adsorbing interface, the chain statistics of an isolated polyelectrolyte chain is not exactly solvable. Using the Debye-Hückel potential for the screened Coulomb interaction among the segments of a flexible chain and a variational procedure, the square of the radius of gyration of the chain was derived as [22]

$$R_g^2 = \frac{L\ell_{eff}}{6}, \quad (2.8)$$

where $\ell_{eff}$ depends on $N, \ell_B$, and $\kappa$ and other excluded volume parameters pertinent to short-range interactions. In deriving the above result, the approximation of uniform expansion was used. For a Gaussian chain, $\ell_{eff}$ is simply the Kuhn length $\ell$. When electrostatic interactions dominate over the short-ranged excluded volume interactions, the limiting behaviors of $\ell_{eff}$ for the low salt and high salt limits were derived by Muthukumar as [22]

$$\ell_{eff} \sim \begin{cases} N & \kappa R_g << 1 \\ \ell_B^{2/5} \kappa^{-4/5} N^{1/5} & \kappa R_g >> 1 \end{cases} \quad (2.9)$$

With this approximation of uniform electrostatic swelling of the chain, Eqs. (2.2)-(2.5) yield

$$\left[ -\frac{\ell_{eff}}{6} \nabla^2_r + \frac{V_s(r)}{k_BT} \right] \psi_m(r) = \lambda_m \psi_m(r), \quad (2.10)$$

where the effective Kuhn length $\ell_{eff}$ absorbs $V_p/k_BT$. As a result, the adsorption criterion for the potential of Eq. (2.7) becomes [22]

$$|\sigma_c| = \frac{\kappa^3 \ell_{eff}}{48\pi \ell_B |q| j_{0,1}}. \quad (2.11)$$
Combining Eqs. (2.9) and (2.10),

\[ |\sigma_c| \sim \begin{cases} \kappa^3 & \kappa R_g << 1 \\ \kappa^{11/5} & \kappa R_g >> 1 \end{cases} \]  

(2.12)

This prediction at higher salt concentrations ($\kappa R_g >> 1$) is consistent with experimental results for planar interfaces [17].

The adsorption of a flexible polyelectrolyte chain onto a spherical vesicle of radius $R$, with the electrolyte concentration being the same both inside and outside, was originally addressed by von Goeler and Muthukumar [23], and the analog of Eq. (2.5) for this situation is

\[
\left[ -\frac{\ell^2}{6} \frac{1}{r^2} \frac{d}{dr} \left( r^2 \frac{d}{dr} \right) + \frac{V_p(r)}{k_B T} + \frac{V_s(r)}{k_B T} \right] \psi_m(r) = \lambda_m \psi_m(r),
\]

(2.13)

where radial symmetry is used and

\[
\frac{V_s(r)}{k_B T} = -4\pi |\sigma_q| \ell B R \sinh(\kappa R) e^{-\kappa r} / \kappa r, \quad r > R
\]

(2.14)

By absorbing the effect of intra-chain electrostatic interaction into the renormalized effective Kuhn length as $\ell_{eff}$, Eq. (2.13) becomes

\[
\left[ -\frac{\ell_{eff}}{6} \frac{1}{r^2} \frac{d}{dr} \left( r^2 \frac{d}{dr} \right) + \frac{V_s(r)}{k_B T} \right] \psi_m(r) = \lambda_m \psi_m(r)
\]

(2.15)

where $V_s(r)$ is given by Eq. (2.14). Using a variational procedure on Eq. (2.15), von Goeler and Muthukumar derived the adsorption criterion as [23]

\[
|\sigma_c| = \frac{\kappa^3 \ell_{eff}}{12\pi \ell_B |q|} \frac{1}{(1 - e^{-2\kappa R})}.
\]

(2.16)
The limits of the dependence of critical surface charge density on the salt concentration follows from Eqs. (2.12) and (2.16) as

\[
|\sigma_c| \sim \begin{cases} 
\kappa^2, & \kappa R \ll 1 \& \kappa R_g \ll 1 \\
\kappa^{6/5}, & \kappa R \ll 1 \& \kappa R_g \gg 1 \\
\kappa^{11/5}, & \kappa R \gg 1 \& \kappa R_g \gg 1 \\
\kappa^3, & \kappa R \gg 1 \& \kappa R_g \ll 1 
\end{cases} 
\] (2.17)

The critical condition \( |\sigma_c| \sim \kappa^{6/5} \) is consistent with the experimental results summarized in Eq. (2.1) for adsorption of synthetic polyelectrolytes on micelles [20, 50–55]. Also, in general, if \( R \gg R_g \), then the limit of planar surface with \( \sigma_c \sim \kappa^3 \ell_{eff} \) is recovered.

The above potential \( V_s(r) \) of Eq. (2.14) is pertinent to the situation of vesicles where the dielectric constant and salt concentration are the same in both the interior and exterior regions. In the limit of vesicle radius \( R_0 \to \infty \), Eq. (2.14) reduces to the result of Eq. (2.6) for planar interfaces. On the other hand, if we were to consider a colloidal situation of adsorption of a polyelectrolyte chain to a spherical solid with no salt inside the sphere, then the potential is given by the Debye-Hückel theory as

\[
\frac{V_s(r)}{k_BT} = \frac{V_{DH}(r)}{k_BT} = -4\pi|\sigma|q\ell\ell BR_0^2 e^{-\kappa(r-R)} (1 + \kappa R) r \quad r > R. 
\] (2.18)

For this potential, it must be noted that the corresponding planar limit \( (R \to \infty) \) is twice the result given in Eq. (2.6). Since the difference between \( V_s(r) \) of Eq. (2.14) and the Debye-Hückel potential is merely in the prefactor (not dependent on \( r \)), the variational result of von Goeler and Muthukumar gives the critical condition for the Debye-Hückel surface potential as

\[
|\sigma_c| = \frac{\kappa^2 \ell_{eff} (1 + \kappa R)}{24\pi \ell B |q| R}.
\] (2.19)
and with the use of Eq. (2.9), we get

\[
|\sigma_c| \sim \begin{cases} 
\kappa^2, & \kappa R \ll 1 \quad \& \quad \kappa R_g \ll 1 \\
\kappa^{6/5}, & \kappa R \ll 1 \quad \& \quad \kappa R_g \gg 1 \\
\kappa^{11/5}, & \kappa R \gg 1 \quad \& \quad \kappa R_g \gg 1 \\
\kappa^3, & \kappa R \gg 1 \quad \& \quad \kappa R_g \ll 1 
\end{cases}
\]

(2.20)

Again, the prediction $|\sigma_c| \sim \kappa^{6/5}$ for salt concentrations pertinent to experimental conditions on adsorption onto solid-like spheres is also consistent with the experimental findings given in Eq. (2.1) [20, 50–55]. These conclusions are also in qualitative agreement with simulation results [36–49]. Therefore, the major conclusions for the dependence of $\sigma_c$ on $\kappa$ are insensitive to whether $V_s(r)$ of Eq. (2.14) or $V_{DH}$ of Eq. (2.18) is used in the variational procedure.

The solution of Eq. (2.13) with $V_p = 0$ and $V_s = V_{DH}$ has been extensively investigated by Cherstvy and Winkler in a series of publications [30–35] using the non-variational procedure of the Wentzel-Kramers-Brillouin (WKB) approximation in quantum mechanics [56]. In addition, they solved Eq. (2.13) exactly by taking $V_p = 0$ and $V_s$ as the Hulthén potential which is an approximation for the Debye-Hückel potential. Based on these analyses, the authors derived the critical condition for adsorption as

\[
|\sigma_c| \sim \begin{cases} 
\kappa, & \kappa R \ll 1 \\
\kappa^3, & \kappa R \gg 1 
\end{cases}
\]

(2.21)

As described above, the intra-chain electrostatic interaction energy $V_p$ must be taken into account for the dependence of $\sigma_c$ on $\kappa$. By simply adopting the procedure of Muthukumar, the above equation becomes
The high salt limit is the same as in the variational theory of von Goeler and Muthukumar. However, there is a discrepancy between the variational theory and the WKB method for the low salt concentration limit. Although the WKB method was used for $V_{DH}$ and not for $V_s$ of Eq. (2.14), we do not expect any change in the scaling laws of Eq. (2.22) for $V_s$ using the WKB method. As discussed below, the variational result is only a bound and the low salt limit requires careful numerical analysis in resolving this discrepancy. However, in the experimentally relevant regime of high salt, both the variational calculation and the numerical WKB methods lead to the same scaling law between $\sigma_c$ and $\kappa$.

For the interior state, where a polyelectrolyte chain adsorbs to the interior surface of the vesicle, the attractive electrostatic potential $V_s(r)$ between the polyelectrolyte and the surface is given by

$$\frac{V_s(r)}{k_BT} = -4\pi|\sigma q|\ell_B R e^{-\kappa R} \frac{\sinh(\kappa r)}{\kappa r}, \quad r < R$$  \hspace{1cm} (2.23)

In obtaining this potential, the salt concentration and the dielectric constant are taken to be the same both inside and outside the vesicle. The combined Eqs. (2.10) and (2.23) were solved by Wang and Muthukumar [24] using a variational method, and the authors identified two regimes of polyelectrolyte encapsulation and preferred radii of vesicles for encapsulation. When $V_s$ is weak, the encapsulation is entropy-dominated and the chain is delocalized inside the vesicle. In this regime, the optimum radius of the encapsulating vesicle decreases with increasing strength of $V_s$. When $V_s$ is strong, the encapsulation is adsorption-dominated and the polyelectrolyte is localized near the interface. In this regime, the optimum radius of the encapsulating
vesicle increases with an increase in the strength of $V_s$. There are no other theoretical calculations for the interior state addressed here, although there have been some interesting work on virus-like particles [9, 12–16]. Since the validity of the variational procedure is questionable for low salt concentrations, we address here the interior state with the WKB approximation and compare with our previous variational results. Accurate calculation of the free energies of the exterior and interior states of adsorbed polyelectrolyte chain allows an understanding of the relative stabilities of these two states in terms of the various parameters $\sigma, q, \ell_B, N, R,$ and $\kappa$.

The outline of the rest of the paper is as follows. Sec. 2.2 describes the model and the theoretical method based on the WKB approximation. In Sec. 2.3, our main results on the exterior state, the interior state, and the exchange between these states are discussed. The main conclusions are summarized in Sec. 2.4.

2.2 Model and Theoretical Method

2.2.1 Polyelectrolyte chain and interacting vesicle

The vesicle is taken as a thin spherical shell of uniform charge density $\sigma e$, with both the interior and exterior regions containing the same salt concentration and hence the same Debye length $\kappa^{-1}$. The radius of the vesicle is $R$. The adsorbing polyelectrolyte chain is taken to be flexible described by the Edwards path integral representation as given by Eq. (2.2) for the probability distribution function $G(\mathbf{r}, \mathbf{r}'; N)$. By integrating out the degrees of freedom of all dissociated small ions and solvent molecules in the system, $V_p[\mathbf{r}(s)]$ in Eq. (2.2) due to the intra-chain inter-segment interactions is given by [22]

$$
\frac{V_p[\mathbf{r}(s)]}{k_B T} = \frac{\ell^3}{2} \int_0^N ds' \left( \frac{1}{2} - \chi \right) \delta \left[ \mathbf{r}(s) - \mathbf{r}(s') \right] + \frac{q^2 \ell_B \ell^2}{2} \int_0^N ds' e^{-\kappa |\mathbf{r}(s) - \mathbf{r}(s')|}.
$$

(2.24)
where the Debye-Hückel theory is assumed to be valid for the dissociated ions. Here \( q \) is the uniform linear charge number density along the chain backbone. If there are \( z_p \) effective charged groups per Kuhn length, then \( q = z_p/\ell \). The first term on the right hand side of Eq. (2.24) represents the usual short-ranged excluded volume interaction, with \( \chi \) being the Flory-Huggins parameter. The potential energy arising from the attractive interaction between the interface and a segment of the polyelectrolyte chain is

\[
\frac{V_s(r)}{k_B T} = \begin{cases} 
-\tilde{V}_0 \frac{B}{\pi} e^{-\kappa (r-R)}, & r > R \\
-\tilde{V}_0 \frac{B}{\pi} \frac{\sinh(\kappa r)}{\sinh(\kappa R)}, & r < R 
\end{cases} \tag{2.25}
\]

where

\[
\tilde{V}_0 = 2\pi |\sigma q| \sqrt{\frac{\ell B}{\kappa}} \left( 1 - e^{-2\kappa R} \right). \tag{2.26}
\]

As already pointed out, Eqs. (2.25) and (2.26) are valid for uniform salt concentration both inside and outside the vesicle and within the Debye-Hückel theory. It is to be noted that \( V_s(r) \) of Eq. (2.25) is continuous at the vesicle interface \( (r = R) \), unlike that of Eq. (2.18), and a plot of \( V_s(r) \) against \( r/R \) is given in Fig. 2.2a for \( \kappa R = 1 \) and 2, as typical examples, in units of \( \tilde{V}_0 \).

As in the original approximate treatment of the intra-chain excluded volume and electrostatic interaction by Muthukumar with a variational procedure, we take these interactions in terms of only a renormalized effective Kuhn length \( \ell_{eff} \) given by [22]

\[
\left( \frac{\ell_{eff}}{\ell} \right)^{5/2} \left( \frac{\ell_{eff}}{\ell} \right)^{3/2} = \frac{4}{3} \left( \frac{3}{2\pi} \right)^{3/2} \left( \frac{1}{2} - \chi \right) \sqrt{N} + \frac{2\sqrt{6}}{3} z_p^2 \ell \ell_{eff} N^{3/2} \frac{a^2 - 4a + 6}{a^{5/2}} e^{a} \text{erfc}(\sqrt{a}) \tag{2.27}
\]

where

\[
a \equiv \kappa^2 R_g^2 \quad \text{with} \quad R_g^2 = \frac{N\ell \ell_{eff}}{6}. \tag{2.28}
\]
Figure 2.2: (a) Reduced potential as a function of the vesicle radius \( R \). (b) Sketch of \( \mathcal{R} \), given by Eq. (2.35), as a function of radius for both inside and outside of the vesicle. I and II refer to \( \mathcal{R} > 0 \) and \( \mathcal{R} < 0 \), respectively, to be distinguished in the WKB method.

As already noted, the limiting values of \( \ell_{\text{eff}} \) for the low-salt and high-salt limits are [22]

\[
\ell_{\text{eff}} = \begin{cases} 
\frac{2}{3} \left( \frac{2}{5} \right)^{2/3} \frac{1}{\pi^{1/3}} \left( \frac{2 \ell_B}{\ell} \right)^{2/3} N \ell, & \kappa R_g << 1 \\
\frac{6^{1/5}}{\pi^{3/5}} \left[ \left( \frac{1}{2} - \chi \right) + \frac{4 \pi z^2 \phi}{\kappa^2 \ell^3} \right]^{2/5} N^{1/5} \ell, & \kappa R_g >> 1 
\end{cases}
\]  

(2.29)
When electrostatic interactions dominate over the short-range excluded volume interaction, the above equation reduces to Eq. (2.9). In the numerical calculations presented in the next section, the full crossover formula, Eq. (2.27), is used.

Using the effective Kuhn length to account for the intra-chain interaction, Eq. (2.10) can be rewritten as

\[
\left[ -\frac{\ell \ell_{eff}}{6} \frac{d}{dx} \left( x^2 \frac{d}{dx} \right) + \frac{V_s(x)}{k_B T \kappa^2} \right] \psi_m(x) = \frac{\lambda_m}{\kappa^2} \psi_m(x) \tag{2.30}
\]

where \( x = \kappa r \). With the change of variable, \( \psi_m = \phi / x \), we get

\[
\frac{d^2 \phi(x)}{dx^2} - \frac{6}{\ell \ell_{eff}} \frac{V_s(x)}{k_B T \kappa^2} \phi(x) = \mu \phi(x), \tag{2.31}
\]

where

\[
\mu = -\frac{6\lambda_m}{\ell \ell_{eff} \kappa^2} \equiv -\lambda. \tag{2.32}
\]

Therefore, in general for both inside and outside the vesicle,

\[
\frac{d^2 \phi(x)}{dx^2} + \mathcal{R}(x) \phi(x) = 0, \tag{2.33}
\]

where

\[
\mathcal{R}(x) = -\frac{6}{\ell \ell_{eff}} \frac{V_s(x)}{k_B T \kappa^2} - \mu \tag{2.34}
\]

Combining Eqs. (2.25) and (2.34),

\[
\mathcal{R}(x) = \begin{cases} 
B \gamma \sinh(\gamma) \frac{2^x - x}{x} - \mu, & x > \gamma \\
B \gamma e^{-\gamma} \sinh(\gamma) \frac{x}{x} - \mu, & x < \gamma 
\end{cases} \tag{2.35}
\]

where \( \gamma = \kappa R \) and

\[
B = \frac{24\pi |\sigma q|}{\kappa_3^3} \frac{\ell_B}{\ell_{eff}}. \tag{2.36}
\]
Our objective is to solve Eq. (2.33) for $\phi(x)$ and get $\psi = \phi/x$, and then $G(r,r'\mid N)$ from Eq. (2.4), from which the adsorption criteria and density profiles are to be computed.

2.2.2 WKB Procedure

We solve Eq. (2.33) using the WKB method [56]. In view of the spatial dependence of $V_s(r)$ given in Fig. 2.2a, a sketch of $\mathcal{R}$ is given in Fig. 2.2b for both inside and outside of the vesicle. For interesting values of $\mu$ given by Eq. (2.32) enabling possibilities of bound states, $\mathcal{R}$ has a simple root ($\mathcal{R} \sim (x - x_0)$) at the turning point $x_0$, as sketched in Fig. 2.2b. For each of the inside and outside regions of the vesicle, there are two scenarios: Region I with $\mathcal{R} > 0$ and Region II with $\mathcal{R} < 0$.

In Region I ($\mathcal{R} > 0$), the WKB solution is [56]

$$\phi_1(x) = \frac{\xi_1^{1/6}}{\sqrt{k_1}} [\alpha_1 \text{Ai}(-z_1) + \beta_1 \text{Bi}(-z_1)], \quad \mathcal{R} > 0 \quad (2.37)$$

where

$$k_1^2 = \mathcal{R}, \quad k_1 > 0 \quad (2.38)$$

$$z_1 = \left(\frac{3}{2}\xi_1\right)^{2/3} \quad (2.39)$$

$$\xi_1 = \begin{cases} 
\int_{x_0}^{x} dx' k_1(x'), & x < \gamma \\
\int_{x_0}^{x_0} dx' k_1(x'), & x > \gamma 
\end{cases} \quad (2.40)$$

and $\text{Ai}$ and $\text{Bi}$ are the Airy functions of first and second kind, respectively [57]. $\alpha_1$ and $\beta_1$ are coefficients to be determined by using boundary conditions.

Analogously in Region II ($\mathcal{R} < 0$), the WKB solution is [56]

$$\phi_2(x) = \frac{\xi_2^{1/6}}{\sqrt{k_2}} [\alpha_2 \text{Ai}(z_2) + \beta_2 \text{Bi}(z_2)], \quad \mathcal{R} < 0 \quad (2.41)$$

where

$$k_2^2 = -\mathcal{R}, \quad k_2 > 0 \quad (2.42)$$
\[ z_2 = \left( \frac{3}{2} \xi_2 \right)^{2/3} \]  
\[ \xi_2 = \begin{cases} 
\int_x^{x_0} dx' k_2(x') & x < \gamma \\
\int_{x_0}^x dx' k_2(x') & x > \gamma 
\end{cases} \]  

and \( \alpha_2 \) and \( \beta_2 \) are coefficients to be determined using the boundary conditions. The unknowns are the coefficients \( \alpha_1, \beta_1, \alpha_2, \) and \( \beta_2, \) and the turning point \( x_0. \) These are determined for the exterior and interior states as follows.

### 2.2.3 Exterior state

For this situation, we follow the same steps taken by Cherstvy and Winkler [20, 30–32, 34, 35, 58] and so only a brief derivation is given here. In this case,

\[ \mathcal{R}(x) = B\gamma \sinh(\gamma) \frac{e^{-x}}{x} - \mu. \]  

Since \( \mathcal{R}(x_0) = 0 \) at the turning point, \( \mu \) is

\[ \mu = B\gamma \sinh(\gamma) \frac{e^{-x_0}}{x_0} \]

so that

\[ \mathcal{R}(x) = B\gamma \sinh(\gamma) \left( \frac{e^{-x}}{x} - \frac{e^{-x_0}}{x_0} \right). \]

As \( Bi(z) \) is an increasing function of \( z \) diverging at \( z \to \infty, \beta_2 \) in Eq. (2.41) must be zero. At the turning point \( x_0, \phi_1(x_0) = \phi_2(x_0), \) and \( \phi'_1(x_0) = \phi'_2(x_0), \) resulting in

\[ \alpha_1 Ai(0) + \beta_1 Bi(0) = \alpha_2 Ai(0) \quad \text{and} \quad -\alpha_1 Ai(0) + \beta_1 Bi(0) = -\alpha_2 Ai(0) \]  

Therefore \( \beta_1 = 0 \) and \( \alpha_1 = \alpha_2. \) As a result,

\[ \phi_1(x) = \frac{\xi_1^{1/6}}{\sqrt{k_1}} \alpha_1 Ai(-z_1), \quad x < x_0 \]
and

\[ \phi_2(x) = \frac{\xi_2^{1/6}}{\sqrt{k_2}} \alpha_1 Ai(z_2), \quad x > x_0 \]  

(2.50)

The only unknown coefficient \( \alpha_1 \) is absorbed into the normalization of the eigenfunction and hence into the density profile. The remaining unknown \( x_0 \) is determined from the boundary condition,

\[ \phi_1(x = \gamma) = 0. \]  

(2.51)

Therefore, it follows from Eqs. (2.49), (2.39), and (2.40) that

\[ Ai(-z_1\gamma) = 0 \]  

(2.52)

where

\[ z_1\gamma = \left( \frac{3}{2} \xi_1\gamma \right)^{2/3}, \quad \xi_1\gamma = \int_\gamma^{x_0} dx' k_1(x'). \]  

(2.53)

Denoting the first zero of \( Ai(-z_1\gamma) \) as \(-a_1\) \((a_1 \simeq 2.33811)\), we get

\[ \int_\gamma^{x_0} dx' \sqrt{\mathcal{R}} = \frac{2}{3} (a_1)^{3/2}. \]  

(2.54)

Substitution of Eq. (2.47) for \( \mathcal{R} \) in Eq. (2.54) yields the desired expression for \( x_0 \) as

\[ \sqrt{B\gamma \sinh(\gamma)} \int_\gamma^{x_0} dx' \left( \frac{e^{-x}}{x} - \frac{e^{-x_0}}{x_0} \right)^{1/2} = \frac{2}{3} (a_1)^{3/2}. \]  

(2.55)

This equation is solved numerically and \( \phi_1 \) and \( \phi_2 \) are computed subsequently. The density profile \( \mathcal{P}(x) = x^2 \psi^2(x) = \phi^2(x) \) is then constructed with the normalization condition

\[ 4\pi \int_\gamma^{\infty} dx \mathcal{P}(x) = 4\pi \int_\gamma^{\infty} dx x^2 \psi^2(x) = 4\pi \int_\gamma^{\infty} dx \phi^2(x) = 1. \]  

(2.56)
The condition for polyelectrolyte adsorption on the exterior surface of the vesicle corresponds to \( \mu = 0 \), that is \( x_0 \to \infty \), according to Eq. (2.46). Therefore, it follows from Eq. (2.55) that the critical condition in terms of \( B_c \) for a given \( \gamma \) is

\[
\sqrt{B_c \gamma \sinh(\gamma)} \int_{\gamma}^{\infty} \frac{dx'}{\sqrt{x'}} e^{-x'/2} = \frac{2}{3} (ai_1)^{3/2}.
\]

so that

\[
B_c = \left( \frac{2}{3} \right)^2 \frac{(ai_1)^3}{2\pi[\text{erfc}(\sqrt{\frac{\gamma}{2}})]^2} \frac{1}{\gamma \sinh(\gamma)}.
\]

Substituting Eq. (2.36) for \( B \), the critical surface charge density for adsorption is

\[
|\sigma_c| = \frac{(ai_1)^3 \kappa^3 \ell_{\text{eff}}}{108 \pi^2 \ell_B |q| \gamma \sinh(\gamma)} \left[ \frac{1}{\text{erfc} \left( \sqrt{\frac{\gamma}{2}} \right)} \right]^2.
\]

The numerically computed results on the density profile and adsorption criteria are discussed in the next section.

### 2.2.4 Interior state

The previous analysis of this situation was performed using only variational methods [24, 25]. Here, we use the WKB method. For this situation,

\[
\mathcal{R}(x) = B \gamma e^{-\gamma \sinh(x)} - \mu.
\]

Defining the turning point \( x_0 \) in terms of \( \mu \),

\[
\mu \equiv B \gamma e^{-\gamma \sinh(x_0)} \frac{\sinh(x_0)}{x_0},
\]

we have

\[
\mathcal{R}(x) = B \gamma e^{-\gamma} \left( \frac{\sinh(x)}{x} - \frac{\sinh(x_0)}{x_0} \right).
\]
Therefore, we get from Eqs. (2.37)-(2.40) and (2.62) valid for Region I ($\mathcal{R} > 0$)

$$\phi_1(x) = \frac{\xi_1^{1/6}}{\sqrt{k_1}} \alpha_1 \left[ Ai(-z_1) + \left( \frac{\beta_1}{\alpha_1} \right) Bi(-z_1) \right], \quad \mathcal{R} > 0 \quad (2.63)$$

where

$$z_1 = \left( \frac{3}{2} \xi_1 \right)^{2/3}, \quad \xi_1 = \int_{x_0}^{x} dx' \left( B \gamma e^{-\gamma} \right)^{1/2} \left[ \frac{\sinh(x)}{x} - \frac{\sinh(x_0)}{x_0} \right]^{1/2}. \quad (2.64)$$

For Region II ($\mathcal{R} < 0$), we get from Eqs. (2.41)-(2.44) and (2.62),

$$\phi_2(x) = \frac{\xi_2^{1/6}}{\sqrt{k_2}} \alpha_2 \left[ Ai(z_2) + \left( \frac{\beta_2}{\alpha_2} \right) Bi(z_2) \right], \quad \mathcal{R} < 0 \quad (2.65)$$

where

$$z_2 = \left( \frac{3}{2} \xi_2 \right)^{2/3}, \quad \xi_2 = \int_{x}^{x_0} dx' \left( B \gamma e^{-\gamma} \right)^{1/2} \left[ \frac{\sinh(x_0)}{x_0} - \frac{\sinh(x)}{x} \right]^{1/2}. \quad (2.66)$$

The objective is to determine the coefficients $\alpha_1, \beta_1, \alpha_2,$ and $\beta_2$ and the turning point $x_0$ appearing in Eqs. (2.63) and (2.65) for $\mathcal{R}$ of Eq. (2.62). This is performed by imposing continuity of $\phi$ and its slope at the turning point $x_0$,

$$\phi_1(x = x_0) = \phi_2(x = x_0) \quad (2.67)$$

$$\phi_1' |_{x \rightarrow x_0} = \phi_2' |_{x \rightarrow x_0} \quad (2.68)$$

and from the boundary conditions

$$\phi(\gamma) = 0; \quad \frac{d\phi_2(x)}{dx} \bigg|_{x \rightarrow 0} = 0 \quad (2.69)$$
and the normalization condition for the density profile,

\[ 4\pi \int_0^\gamma dx \, \phi^2(x) = 1. \]  \hspace{1cm} (2.70)

Now, \( \phi_1(x_0) \) is given by Eq. (2.63) as

\[ \phi_1(x_0) = C_1 Ai(0) \left( \alpha_1 + \sqrt{3} \beta_1 \right) \]  \hspace{1cm} (2.71)

where we have used \( Bi(0) = \sqrt{3} Ai(0) \) and

\[ C_1 = \lim_{x \to x_0} \frac{\xi_1^{1/6}}{\sqrt{k_1}} = \left( \frac{2}{3} \right)^{1/6} \left( \frac{1}{R'_{|x_0}} \right)^{1/6}. \]  \hspace{1cm} (2.72)

Similarly \( \phi_2(x_0) \) follows from Eq. (2.65) as

\[ \phi_2(x_0) = C_2 Ai(0) \left( \alpha_2 + \sqrt{3} \beta_2 \right) \]  \hspace{1cm} (2.73)

where

\[ C_2 = \lim_{x \to x_0} \frac{\xi_2^{1/6}}{\sqrt{k_2}} = \left( \frac{2}{3} \right)^{1/6} \left( \frac{1}{R'_{|x_0}} \right)^{1/6} = C_1. \]  \hspace{1cm} (2.74)

Therefore, the continuity condition \( \phi_1(x_0) = \phi_2(x_0) \) yields from Eqs. (2.67) and (2.73)

\[ \alpha_1 - \alpha_2 + \sqrt{3}(\beta_1 - \beta_2) = 0. \]  \hspace{1cm} (2.75)

The derivative \( \phi'_1(x) \) from Eq. (2.63) is

\[ \phi'_1(x) = \left\{ \frac{1}{6} \frac{\xi_1'}{\xi_1} \frac{1}{2} \frac{k_1'}{k_1} \right\} \phi_1(x) \]  \hspace{1cm} (2.76)

where the prime denotes the derivative \( d/dx \). Taking the limit \( x \to x_0 \) and noting

\[ \lim_{x \to x_0} \left( \frac{1}{6} \frac{\xi_1'}{\xi_1} \frac{1}{2} \frac{k_1'}{k_1} \right) = - \frac{1}{6} \frac{\xi_1'}{R} \bigg|_{x \to x_0} \equiv C_3 \]  \hspace{1cm} (2.77)
we get from Eqs. (2.40), (2.63), (2.74), and (2.77)

\[ \phi_1'(x = x_0) = C_3 \phi_1(x_0) - \left( \frac{-\alpha_1 + \sqrt{3} \beta_1}{3^{1/3} \Gamma(1/3)} \right) \left( \frac{2}{3} \right)^{1/3} \frac{1}{C_1} \]  

(2.78)

where the values of the Airy functions for zero argument have been used. \( \Gamma(1/3) \) is the Gamma function, \( \Gamma(1/3) \approx 2.6789 \). By following the same procedure for \( \phi_2(x) \) of Eq. (2.65)

\[ \phi_2'(x) = \begin{cases} 
\frac{1}{6} \xi_2' - \frac{1}{2} k_2' + \frac{\alpha_2 Ai'(z_2) + \beta_2 Bi'(z_2)}{[\alpha_2 Ai(z_2) + \beta_2 Bi(z_2)]} \xi_2' \left( \frac{3}{2} \xi_2 \right)^{1/3} \end{cases} \phi_2(x). \]  

(2.79)

At the turning point \( x = x_0 \)

\[ \phi_2'(x = x_0) = C_3 \phi_2(x_0) - \left( \frac{-\alpha_2 + \sqrt{3} \beta_2}{3^{1/3} \Gamma(1/3)} \right) \left( \frac{2}{3} \right)^{1/3} \frac{1}{C_1} \]  

(2.80)

The continuity conditions \( \phi_1'(x = x_0) = \phi_2'(x = x_0) \) and \( \phi_1(x = x_0) = \phi_2(x = x_0) \) yield from Eqs. (2.78) and (2.80)

\[ -\alpha_1 + \sqrt{3} \beta_1 = -\alpha_2 + \sqrt{3} \beta_2. \]  

(2.81)

Combining Eqs. (2.75) and (2.81), we get

\[ \alpha_1 = \alpha_2 = \alpha \quad \text{and} \quad \beta_1 = \beta_2 = \beta \]  

(2.82)

Using the boundary condition \( \phi_1(\gamma) = 0 \), Eqs. (2.63) and (2.64) give

\[ \frac{\beta}{\alpha} = - \frac{\text{Ai} \left[- \left( \frac{3}{2} \xi_1(x = \gamma) \right)^{2/3} \right]}{\text{Bi} \left[- \left( \frac{3}{2} \xi_1(x = \gamma) \right)^{2/3} \right]}, \]  

(2.83)
as a function of $x_0$. From the other boundary condition, $(d\phi_2(x)/dx)_{x \to 0} = 0$, Eq. (2.80) yields

$$
\frac{1}{6} \left( \frac{3}{2} \right)^{1/3} \xi_2^{-2/3} (x \to 0) = -\frac{\left[ \text{Ai}'(z_{20}) + \frac{\beta}{\alpha} \text{Bi}'(z_{20}) \right]}{\left[ \text{Ai}(z_{20}) + \frac{\beta}{\alpha} \text{Bi}(z_{20}) \right]},
$$

where

$$
z_{20} = \left( \frac{3}{2} \xi_{20} \right)^{2/3}, \quad \xi_{20} = (B\gamma e^{-\gamma})^{1/2} \int_0^{x_0} dx' \left[ \frac{\sinh(x_0)}{x_0} - \frac{\sinh(x')}{x'} \right]^{1/2}.
$$

Combining Eqs. (2.63), (2.65), (2.83), and (2.84), the eigenfunction $\phi$ is computed numerically and the density profiles constructed.

The critical condition for adsorption inside the vesicle is given by the minimum value $B_c$ of the quantity $B = 24\pi\ell_B|\sigma_q|/\kappa^3\ell_{eff}$ above which there are solutions to Eqs. (2.63) and (2.65). In general, for $B > B_c$, there can be more than one solution satisfying the boundary conditions. However, only one of these solutions satisfies the physical result of the density profile being non-zero everywhere inside the vesicle. For $B < B_c$, there are no solutions to Eqs. (2.63) and (2.65). The methodology of computing $B_c$ is as follows. The critical adsorption condition for the polymer inside the sphere is defined as the minimum value of $B$ for a given $\gamma$ at which the turning point, $x_0$, is at the center of the sphere. Although this does not define the condition of $\mu = 0$, it gives a minimal value for it. To get this critical value, $B_c$, we use the two boundary conditions for the density profile. Adsorbing boundary condition of the surface, $\phi(\gamma) = 0$, gives us the value of one of the coefficients, namely $\beta$. Since the density profile should be smooth at $x = 0$, we take $\phi(0) = 0$. This condition is satisfied only when $B$ is some discrete value for a given $\gamma$. The minimum and positive value of $B$ is the critical condition.
2.3 Results and Discussion

Using the equations derived above, we have computed the density profiles and adsorption criteria for the exterior and interior states. One of the key quantities which appears in these equations is the effective Kuhn length representing the electrostatic swelling of the chain due to intra-chain interactions. This is presented first. Next, the density profiles and adsorption criteria are discussed. Finally the free energy of the system and the relative stabilities of the exterior and interior states are discussed.

2.3.1 Electrostatic swelling of an isolated chain

As shown in Eqs. (2.27)-(2.29), \( \ell_{\text{eff}} \) depends on \( \chi, \ell_B, \kappa, q = z_p/\ell, \) and \( N \). The full crossover behavior is given in Fig. 2.3, where \( \ell_{\text{eff}} \) is plotted against \( \kappa \ell \) for \( N = 100, \chi = 0.1, \) and \( z_p = 1 \). All lengths are in units of the bare Kuhn length \( \ell \). The dotted lines correspond to the limiting behaviors for low salt (red) \((\kappa R_g << 1)\), and high salt (blue) \((\kappa R_g >> 1)\), given by Eq. (2.29). While the asymptotic results are used in drawing qualitative conclusions, the full crossover is used in all numerical results discussed below.

2.3.2 Density profiles

The density profile \( \mathcal{P}(x) = \phi^2(x) \) for the exterior state is given by Eqs. (2.49), (2.50) and (2.56) as

\[
\mathcal{P}(x) = N \begin{cases} 
\frac{\xi_1^{1/3}(x)}{\sqrt{R}} Ai^2\left(-(3\xi_1/2)^{2/3}\right), & x < x_0 \\
\frac{\xi_2^{1/3}(x)}{\sqrt{-R}} Ai^2\left((3\xi_2/2)^{2/3}\right), & x < x_0 
\end{cases}
\]

(2.86)

with \( R \) given by Eq. (2.35). The normalization constant \( N \) is determined from the normalization condition of Eq. (2.56). Defining the radial distance \( X \) away from the surface of the vesicle,

\[
\kappa X = x - \gamma = \kappa(r - R),
\]

(2.87)
the density profile $\mathcal{P}$ is plotted in Fig. 2.4 as a function of $X$ for a set of vesicle radii at fixed interaction strength $B = 100$ and for a set of interaction strength $B$ at fixed vesicle radius ($\gamma = 4$). As seen in Fig. 2.4a, the density profile is independent of the vesicle radius for $B = 100$. On the other hand, $\mathcal{P}$ is strongly dependent on $B$ for $\gamma = 4$, as shown in Fig. 2.4b. As expected, as the attractive interaction strength parameter $B$ increases, the polymer is closer to the surface. These profiles are entirely equivalent to the variational results for the same $V_s$ and the WKB results for $V_{DH}$.

For the scenario of adsorption on the inside surface of the vesicle, the density profile $\mathcal{P} = \phi^2(x)$ is given by

$$
\mathcal{P} = \mathcal{N} \begin{cases} 
\frac{\xi_1^{1/3}(x)}{\sqrt{\mathcal{R}}} \left( \text{Ai} \left[ -\left( \frac{3\xi_1}{2} \right)^{2/3} \right] + \frac{\beta}{\alpha} \text{Bi} \left[ -\left( \frac{3\xi_1}{2} \right)^{2/3} \right] \right)^2, & x > x_0 \\
\frac{\xi_2^{1/3}(x)}{\sqrt{-\mathcal{R}}} \left( \text{Ai} \left[ \left( \frac{3\xi_2}{2} \right)^{2/3} \right] + \frac{\beta}{\alpha} \text{Bi} \left[ \left( \frac{3\xi_2}{2} \right)^{2/3} \right] \right)^2, & x > x_0 
\end{cases}
$$

(2.88)

where $\mathcal{R}$ is given by Eq. (2.62), and the normalization constant is determined from Eq. (2.70). Following the computational protocol described in the preceding section,
Figure 2.4: The density profile of the polymer in the exterior region, $\varphi^2 = \mathcal{P}$, as a function of $\kappa X$ with $X$ being the distance from the interface: (a) Three different values of $\gamma$ for $B = 100$. (b) Three different values of the strength of the potential, $B$, for $\gamma = 4$.

Some examples of the density profile are given in Fig. 2.5, where $\mathcal{P}$ is plotted against the distance $\kappa X = \kappa(R - r)$ from the surface of the vesicle towards its center. As seen in Fig. 2.5a, for $B = 100$, the density profile is closer to the surface for higher values of the vesicle radius, essentially independent of $\kappa R$. On the other hand, for
smaller vesicles, the chain is more spread out into the interior. Similarly for a given value of $\gamma = 4$, the polymer is adsorbed closely at the interface as the strength of the interaction between the polymer and the interface is increased, as shown in Fig. 2.5b. These results are in excellent agreement with the variational results presented earlier.
2.3.3 Adsorption criteria

The WKB result of the adsorption criterion for the exterior state is given by Eq. (2.59) as

\[ |\sigma_c| = \frac{(ai_1)^3}{108\pi^2} \frac{\kappa^2 \ell_{eff}}{\ell_B |q| R} \frac{1}{\sinh(\kappa R)} \left[ \frac{1}{\text{erfc} \left( \sqrt{\frac{\kappa R}{2}} \right)} \right]^2. \]  

(2.89)

The asymptotic limits of this WKB result for the low salt ($\kappa R_g << 1$) and high salt ($\kappa R_g >> 1$) limits are

\[ |\sigma_c| = \frac{|ai_1|^3 \ell_{eff}}{108\pi^2 \ell_B |q|} \begin{cases} \frac{\kappa}{R^2}, & \kappa R << 1 \\ \pi \kappa^3, & \kappa R >> 1 \end{cases} \]  

(2.90)

When the $\kappa$-dependence of $\ell_{eff}$ is taken into account from Eq. (2.29), the above equation gives

\[ |\sigma_c| \sim \begin{cases} \kappa, & \kappa R << 1 \\ \kappa^{11/5}, & \kappa R >> 1 \end{cases} \]  

(2.91)

The calculated results for the critical surface charge density, above which there is adsorption in the exterior state, from Eqs. (2.27) and (2.91), are given in Fig. 2.6a. Here $24\pi |\sigma_c| q \ell_B$ is plotted against $\kappa$ for different values of the vesicle radius $R$. The full crossover formula for $\ell_{eff}$ is used in getting these results. As seen in Fig. 2.6a, the critical charge density crosses over from $\sigma_c \sim \kappa$ behavior at small values of $\kappa R$ to $\sigma_c \sim \kappa^{11/5}$ behavior at large values of $\kappa R$. The values 1 and 11/5 are the bounds for the exponent $a$ of Eq. (2.1). The apparent value around 6/5 is in the crossover region.

Thus there is no difference between the WKB result and the variational result of Eq. (2.21) for high salt concentrations. However, in the low salt limit, which is not readily accessible to experiments, there is a discrepancy between the variational result $\sigma_c \sim \kappa^2$ and the WKB result $\sigma_c \sim \kappa$, as already pointed out by Cherstvy and
Figure 2.6: Critical charge $24\pi|\sigma_c q|\ell_B$ as a function of $\kappa\ell$. (a) Outside the sphere, all curves approach the asymptotic limit of a planar surface, $\kappa R >> 1$. (b) Inside the sphere, the critical conditions are given for values of vesicle radius from $R = 40\ell$ (top curve) to $R = 190\ell$ (lowest curve), with the asymptotic limit denoted by the black line with a slope of $5/2$.

Winkler [20]. This discrepancy can be traced to the numerical difficulty in identifying the critical condition in the variational procedure of von Goeler and Muthukumar for the limit of $\kappa \to 0$. In addition, the variational procedure gives a bound and the numerical values of $\sigma_c$ from the WKB method are bounded by the variational result.
This difference goes away at higher salt concentrations of experimental relevance, and in fact both the WKB and the variational calculations give equivalent results ($\sigma_c \sim \kappa^{11/5}$) within a numerical factor of order unity.

For the interior state, the critical condition of adsorption is computed by finding the minimum value $B_c = 24\pi\ell B(|\sigma q|)/\kappa^3\ell_{eff}$ below which there are no solutions to Eqs. (2.63) and (2.65). A plot of $24\pi\ell^2|\sigma q|\ell_B$ versus $\kappa$ is given in Fig. 2.6b for different values of the vesicle radius $R$ (from $40\ell$ to $190\ell$). For all values of $R$, $\sigma_c$ approaches an asymptotic behavior as illustrated by the solid line in the figure, corresponding to $\gamma = \kappa R \sim 5 - 10$. For smaller values of $\kappa R$, there is a deviation from the asymptotic behavior with a weaker dependence of $\sigma_c$ on $\kappa$. In the asymptotic limit (high salt concentration, $\kappa R \geq 5$, the slope of the solid line is close to $5/2$,

$$|\sigma_c| \sim \kappa^{5/2}.$$  \hspace{1cm} (2.92)

This result is in very good agreement with the result of variational calculation of Ref. [23].

### 2.3.4 Free energy of adsorption

The entropic and energy contributions to the free energy of the adsorbed chain can be calculated from the equation for the eigenfunction $\phi(x)$ by following the procedure given in Refs. [24] and [25]. For the exterior state, Eqs. (2.31) and (2.35) give

$$\frac{\partial^2 \phi(x)}{\partial x^2} - B\gamma \sinh(\gamma) \frac{e^{-x}}{x} = -\lambda \phi(x), \quad x > \gamma \hspace{1cm} (2.93)$$

where $x = \kappa r$, $\gamma = \kappa R$, $\lambda = 6\lambda_0/(\kappa^2\ell_{eff})$, and $B = 24\pi|\sigma q|\ell_B/(\kappa^3\ell_{eff})$. Multiplying Eq. (2.93) by $\phi(x)$ and integrating over $x$, and in view of the normalization condition for the density profile, we get

$$\lambda = \lambda_u + \lambda_s \hspace{1cm} (2.94)$$
where the energy part of the free energy is

\[ \lambda_u = -B \gamma \sinh(\gamma) \int_0^\gamma dx \phi^2(x) \frac{e^{-x}}{x}, \]  \hspace{1cm} (2.95)

and the entropic part of the free energy is

\[ \lambda_s = -\int_\gamma^\infty dx \phi(x) \frac{\partial^2}{\partial x^2} \phi(x). \]  \hspace{1cm} (2.96)

The contributions from the energy and entropy to the total free energy of the exterior state are given in Fig. 2.7, as a function of \( \gamma = \kappa R \) for two examples of the polymer-surface interaction energy parameter \( B = 400 \), and 2000. As expected from the reduction of conformational entropy of the chain in the adsorption process, the entropic part \( \lambda_s \) (data in red with the ordinate on the right hand side) is positive and is roughly independent of the vesicle radius. On the other hand, the energy part \( \lambda_u \) (data in blue) is considerably larger than \( \lambda_s \) and is inevitably close to the total free energy \( \lambda \) (data in black). These features are observed for both \( B = 400 \) and \( B = 2000 \), except that the energy contribution to the free energy is much stronger for higher values of the strength of the polymer-surface interaction. The dependence of the total free energy on the vesicle radius is monotonic and the free energy of the adsorbed exterior state decreases continuously with a decrease in the curvature of the vesicle.

The decomposition of the free energy into the energy and entropy contributions can be similarly accomplished for the interior state as well. Now, Eqs. (2.31) and (2.35) give

\[ \frac{\partial^2 \phi(x)}{\partial x^2} - B \gamma e^{-\gamma} \frac{\sinh(x)}{x} \phi(x) = -\lambda \phi(x), \hspace{1cm} x < \gamma \]  \hspace{1cm} (2.97)

where the various symbols are already defined. Multiplying Eq. (2.97) by \( \phi(x) \) and integrating over \( x \), and in view of the normalization condition of Eq. (2.70), we get
Figure 2.7: The entropic part, energy part, and the total free energy of the system, $\lambda_s$, $\lambda_u$, and $\lambda$, respectively, in the exterior state, as a function of $\kappa R$ for two values of the strength of the potential, $B$: (a) $B = 400$, and (b) $B = 2000$.

\[ \lambda = \lambda_u + \lambda_s \] with the energy part given by

\[ \lambda_u = -B \gamma e^{-\gamma} \int_0^\gamma dx \phi^2(x) \frac{\partial^2}{\partial x^2} \frac{\sinh(x)}{x}, \] \hspace{1cm} (2.98)

and the entropy part given by
Figure 2.8: The free energy of the polyelectrolyte chain inside the vesicle, $\lambda$, and its energy and entropic parts, $\lambda_u$ and $\lambda_s$, as a function of $\kappa R$. (a) $B = 400$, and (b) $B = 2000$.

$$\lambda_s = - \int_0^\gamma dx \phi(x) \frac{\partial^2}{\partial x^2} \phi(x).$$  \hspace{1cm} (2.99)

The total free energy and the contributions from energy and entropy are given in Fig. 2.8 as functions of $\gamma = \kappa R$, for two illustrative values of $B$. By considering the case of $B = 400$ (Fig. 2.8a), the entropic part $\lambda_s$ (data in red with the ordinate on...
the right hand side) is positive as expected due to reduction of chain conformations. Also, $\lambda_s$ increases monotonically as $\kappa R$ is increased, eventually reaching an asymptotic value (comparable to the value for the exterior state in this limit). On the other hand, the energy contribution $\lambda_u$ (data in blue) is negative and is an order of magnitude stronger than $\lambda_s$, thus dominating its contribution to the total free energy (data in black). More significantly, the free energy and $\lambda_u$ is non-monotonic with $\kappa R$ as was obtained by the variational calculation in Ref. [16]. The free energy of the vesicle with the chain adsorbed inside is a minimum at an optimum value of the ratio of vesicle radius to the Debye length, denoted by $\kappa R^\ast$. The same features are seen for higher strengths of polymer-surface interaction as shown in Fig. 8b for $B = 2000$, except that the free energy minimum is shifted towards a higher value of $\kappa R^\ast$. The dependence of $\kappa R^\ast$ on the strength parameter $B$ is given in Fig. 2.9 which shows approximately a logarithmic dependence,

$$\kappa R^\ast = 0.65 \log_{10} B - 0.14. \quad (2.100)$$

Therefore, there exists an optimum radius of vesicle for adsorption of a polyelectrolyte chain on its inside surface for a given set of parameters. As long as the adsorption criterion is met, all vesicle radii have net negative free energy and hence the adsorbed encapsulation is a thermodynamically favorable process. However, if the vesicle radius is allowed to vary, then the vesicle with the adsorbed chain is expected to adapt itself towards the global free energy minimum corresponding to $\kappa R^\ast$. The optimum vesicle radius $R^\ast$ depends on $\kappa$ and other parameters such as $\sigma, q, \ell_B$, and $N$ through $B$, as given by Eq. (2.36). Any of these parameters can be used to tune the optimum vesicle radius for encapsulating a flexible polyelectrolyte chain as an adsorbed interior state.
2.3.5 Stabilities of exterior and interior states

The free energy $F$ (in units of $k_B T$) is related to the eigenvalue $\lambda$ by Eqs. (2.32) and (2.33) as

$$F = \frac{\kappa^2 \ell \ell_{\text{eff}}}{6} \lambda. \quad (2.101)$$

From the values of $\lambda$ in the exterior and interior regions, the free energy change can be computed. We define the relative thermodynamic stabilities of the interior and exterior states by defining the change in free energy associated with the exchange of an adsorbed chain from the interior to the exterior region as

$$\Delta F = F_{\text{exterior}} - F_{\text{interior}}. \quad (2.102)$$
\(\Delta F_u\) and \(\Delta F_s\) as the corresponding values of the energy and entropy contributions to the change in free energy. In our definition, all parameters are the same for the initial and final states. Representative results are given in Fig. 2.10a for \(B = 400, \ell_B/\ell = 1,\) and \(N = 100,\) where \(\Delta F, \Delta F_u,\) and \(\Delta F_s\) are plotted against \(R.\) As is evident from the figure, an encapsulated adsorbed chain inside a vesicle is more stable than the ejected adsorbed chain on the exterior surface of the vesicle. Therefore, energy must be supplied to eject the adsorbed chain out of the vesicle. This free energy cost decreases monotonically with \(R,\) when all other parameters are fixed. The precise value of the energy cost depends on the values of all relevant parameters and can be computed using the computational protocol described above. For aqueous systems with \(\sigma = 0.2/nm^2, q = 1/nm,\) and \(c_s = 2mM,\) \(\Delta F\) values are comparable to a few \(k_B T\) as shown in Fig. 2.10a.

An alternative scenario to the case of Fig. 2.10a, where \(R\) is fixed for both the initial and final states, is to consider the initial state corresponding to the optimum vesicle radius \(R^*\) and the final state to be with the vesicle radius \(R.\) The dependencies of \(\Delta F^*, \Delta F_u^*,\) and \(\Delta F_s^*\) on \(R,\) corresponding to this alternate scenario, are given in Fig. 2.10b. Here, the initial value of the vesicle radius is \(R^* = 12.9nm\) and the vesicle radius in the final state is \(R.\) Again, \(\Delta F_u^*\) is the dominant contributor to \(\Delta F^*.\) The entropic part \(\Delta F_s^*\) is essentially independent of \(R.\) Furthermore, \(\Delta F^*\) decreases continuously with \(R\) if \(R > R^*\) and increases continuously with \(R\) if \(R < R^*.\) These results suggest that the free energy cost to eject an adsorbed chain on the inside of a vesicle into the exterior adsorbed state can be mitigated if the vesicle can spontaneously expand into bigger radii. Again, for aqueous systems with \(\sigma = 2/nm^2, q = 1/nm,\) and \(c_s = 2mM,\) \(\Delta F\) values are comparable to a few \(k_B T\) as shown in Fig. 2.10b. The above calculations can be readily repeated to compute the free energy cost associated with the chain expulsion when another variable such as \(T, \sigma, q, \epsilon\) or \(c_s\) is tuned. As an example, the dependencies of \(\Delta F, \Delta F_u,\) and \(\Delta F_s\)
Figure 2.10: The free energy difference of the polyelectrolyte translocation from a vesicle for the strength of the potential, $B = 400$. $\Delta F$ is the total free energy difference, while $\Delta F_u$ and $\Delta F_s$ are the energy and entropic parts for $c_s = 2mM, \sigma = 0.2/nm^2$, and $q = 1/nm$. (a) Vesicle radius is held constant. (b) The initial vesicle radius is the optimum radius, $R^* = 12.9nm$ and the final vesicle radius can be different from $R^*$.

on the salt concentration are given in Fig. 2.11 for $R = 20nm, \sigma = 0.2/nm^2$, and $q = 1/nm$. The free energy difference is seen to decrease with salt concentration and the magnitude is of the order of thermal energy, $k_BT$. 

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2.4 Conclusions

Using the WKB method, we have derived adsorption criteria and density profiles for a flexible polyelectrolyte chain adsorbing to the interior and exterior surfaces of a charged vesicle with uniform surface charge number density $\sigma$. The other experimentally controllable variables used in the derivation are the polymer linear charge number density, polymer length, vesicle radius, the Debye length $\kappa^{-1}$, and the Bjerrum length $\ell_B$. The ionic strength and the dielectric constant of the medium are taken to be the same in both the interior and exterior regions of the vesicle, without regard to the Donnan equilibrium. The intra-chain electrostatic interaction among various segments is also included in deriving the final expressions.

For adsorption inside the vesicle, two regimes are identified as in our earlier variational theory. For weaker polymer-interface attraction, the polymer is unadsorbed.
and is merely delocalized inside the vesicle. For strong enough attraction with the interface, the chain is in an adsorbed state. The adsorption criterion is written in terms of the critical surface charge number density $\sigma_c$ as

$$|\sigma_c| \simeq 0.95 \frac{1}{24\pi \ell^2 |q| \ell_B} \kappa^{5/2}, \quad (2.103)$$

in the high salt limit of $\kappa R \geq 5$. The adsorption occurs for $|\sigma| > |\sigma_c|$, which can be tuned by any of the variables $q, \ell_B$, and $\kappa$. In addition, we find that there is an optimum vesicle radius for forming an adsorbed interior state.

For adsorption outside the vesicle, the critical surface charge density required for adsorption in experimentally relevant conditions where there is a finite amount of electrolyte ions is given by

$$|\sigma_c| \sim \kappa^a, \quad (2.104)$$

where

$$a = \begin{cases} 
\frac{6}{5}, & \kappa R < 1 \quad \& \quad \kappa R_g > 1 \\
\frac{11}{5}, & \kappa R > 1 \quad \& \quad \kappa R_g > 1 \\
3, & \kappa R > 1 \quad \& \quad \kappa R_g < 1 
\end{cases} \quad (2.105)$$

with $R$ and $R_g$ being the vesicle radius and the radius of gyration of the polyelectrolyte chain, respectively. These conclusions for the exterior state are valid also for adsorption to spherical solid-like particles or proteins, except that the numerical prefactor in the scaling law of Eq. (2.103) is different. This difference in the numerical prefactor arises from the difference between $V_s$ of Eq. (2.14) and the Debye-Hüchel potential of Eq. (2.18).

The experimental results summarized in Eq. (2.1) are obtained under the conditions satisfying $\kappa R < 1$ and $\kappa R_g > 1$. Therefore, our theoretical result, $|\sigma_c| \sim \kappa^{6/5}$ appears to be in agreement the experimental results. In general, the results for the interior state from the WKB and variational methods are equivalent, except for a
slight difference of order unity in the numerical prefactors. For the exterior state, similar agreement is seen except in the narrow region of zero-salt limit.

The entropic and energy contributions to the free energy of the adsorbed chain is calculated for both the interior and exterior states. The energy contribution dominates over the entropic part by an order of magnitude. Using the free energy of the chain in these two states, we find that the interior state is more stable and that the energy cost to eject the chain to the exterior with chain adsorption decreases monotonically with the size of the vesicle and also with salt concentration. The unloading of the polymer from a vesicle with its initial optimum radius can be facilitated by allowing the vesicle to expand. The typical values of the free energy cost are comparable to a few $k_BT$.

The theory and calculations presented here are based on an idealized model. Several extensions such as the incorporation of the elasticity of the vesicle surface and the Donnan equilibrium for partitioning of electrolyte ions, and kinetics of ejection of the polymer are of further interest.
CHAPTER 3
DYNAMICS OF COMPLEXATION OF TWO OPPOSITELY CHARGED POLYLECTROLYTES

3.1 Introduction

Oppositely charged polyelectrolytes (PE) in a solution, due to the electrostatic interaction between the their monomers, can form a polyelectrolyte complex (PEC). Some of the applications of PECs in biophysics and material science are flocculation and gene therapy. In 1917, Smoluchowski [59] studied the coagulation of particles and calculated the coagulation rate for neutral particles to be

\[ R(t) = 4\pi r D \left[ 1 + r/\sqrt{\pi D t} \right]. \]

\( r \) is the radius of the particles and the diffusion coefficient is \( D = \frac{k_B T}{6\pi \eta r} \) and \( \eta \) being the viscosity of the solvent. One of the pioneering works on the coagulation of charged particle was done by Onsager [60] at 1934, who applied stochastic methods to solve the Smoluchowski equation [61] for the dissociation of charged particles in the presence of an external electric field. In another study, Debye [62] calculated the rate of the coagulation of a colloid suspension. His results showed that for a system of particles, the capture rate in the steady-state solution for coagulation in diffusion-limited reaction is

\[ C(r) = \frac{4\pi D l_B}{\exp[l_B/r] - 1}. \] (3.1)
There have been other studies regarding complexation process of particles [63–69]. In late 1970s, Hong and Noolandi [66–68] and Rice et al. [69] used Fourier and Laplace transform to find the general solution for the complexation of charged particles in a system. Hong and Noolandi [66] solved the time dependent Smoluchowski equation for particles which interacting with each other in the form of coulomb potential. They considered a general boundary condition and approximated the reaction rate as well as survival probability. Rice et al. [69] studied the reaction rate for oppositely charged ions in an aqueous medium to create an ion pair with partially reflecting boundary condition.

Since polyelectrolytes are a long chain of charged monomers distributed randomly, theoretical studies of polyelectrolyte complexes are extremely complicated. Although the experiments involving these complexes involve a large quantity of polyelectrolytes, for theoretical studies and simulations, investigating a system of 2 or a few polymers next to each other gives us a general understanding of the complexation process and how the complexation process depends on the physical variables such as polymer length and salt concentration. Also, these results can be used to get the statistical behavior of the complexation process between a large amounts of polyelectrolytes. A schematic of the complexation of (a) two ions and (b) two polyelectrolytes is shown in Fig. 3.1.

The polyelectrolyte complexation have been investigated in various simulation researches [70–74]. Peng and Muthukumar [74] have studied the process of substituting a larger polyelectrolyte in a complexation of two polyelectrolytes. They also simulated the complexation of two polyelectrolytes. Their results for the complexation showed that when two polymers get closer to each other than a certain distance, $R_c$, they spontaneously create a polyelectrolyte complex. This distance is independent of
In this study, we investigate the kinetics of the complexation between two oppositely charged polyelectrolytes. In Sec. 3.2 we build a mathematical model for a pair of oppositely charged polyelectrolytes in a solution with salt concentration $c_s$. By employing the Smoluchowski equation [61, 75, 76], we get the probability distribution of the distance of the center of masses of the polyelectrolytes. We investigate the steady-state solution and analyze the dynamics of the complexation process in Sec. 3.3. In the steady-state, we study the effect of the salt concentration on the complexation and the capture rate. We then investigate the mean distance between polyelectrolytes at different salt concentrations and initial distances. Our results shows that this mean distance reaches an equilibrium value in a very short time frame, regardless of the initial distance, $r_0$, or salt concentration. However, the reaction rate and the half-time of the complexation are dependent on $r_0$ and $c_s$. Finally, in Sec. 3.4 we summarize our results.
3.2 Model

The position of any particle in a solution conforms a random walk path due to its diffusion as it was described in Chapter 1 (for more information, see [77]). If the particle is under the influence of an external potential, \( w(\mathbf{r}, t; \mathbf{r}_0) \), which is the probability of finding the particle at \( \mathbf{r} \) at time \( t \), given that it was initially at \( \mathbf{r}_0 \) is defined by the Smoluchowski equation [61, 75–77]

\[
\frac{\partial w(\mathbf{r}, t|\mathbf{r}_0)}{\partial t} = D \nabla^2 w(\mathbf{r}, t|\mathbf{r}_0) - D \nabla \cdot \left( \frac{\nabla V(\mathbf{r})}{k_B T} w(\mathbf{r}, t|\mathbf{r}_0) \right)
\]

(3.2)

with \( D \) being the diffusion coefficient (see 1.2). \( k_B \) and \( T \) are the Boltzmann constant and absolute temperature. The first term in the right side of Eq. (3.2) is diffusion, while the second one, the drift term, is due to the external potential. Eq. (3.2) can be written in the compact form

\[
\frac{\partial w(\mathbf{r}, t|\mathbf{r}_0)}{\partial t} = D \nabla \left[ e^{\frac{V(\mathbf{r})}{k_B T}} \nabla \left( e^{-\frac{V(\mathbf{r})}{k_B T}} w(\mathbf{r}, t|\mathbf{r}_0) \right) \right].
\]

(3.3)
A polyelectrolyte solution contains a large quantity of polymers, in which every monomer interacts with all others. Internal interactions between the monomers of any individual polymer defines the structure of the polyelectrolyte, but does not move the center of mass of the polymer. However, interactions between monomers of different polymers can be defined as an external potential which affects the position of the center of mass. As we described previously, the intra-chain interactions can be absorbed into Kuhn length using self-consistent field theory [3, 22]. Even with this simplification, the time-dependent behavior of a polyelectrolyte solution is too complicated. To analyze the time-dependent solution, we investigate a more fundamental case, which is more theoretically approachable, of complexation of only two oppositely charged polyelectrolytes. This can give us insights on the complexation process. Also, it is possible to apply statistical mechanics methods to investigate larger systems. Another approach is to study this system, when it is at the steady-state. This is specifically helpful to understand the effect of length parameters in the complexation.

First, we calculate the interacting potential between two oppositely charged Gaussian polymers. Then, we investigate the steady-state solution of the Smoluchowski equation for a polymer undergoing such a potential. Finally, we study the dynamics of the complexation of the polyelectrolytes. We introduce a comoving coordinate system, of which the origin is at the center of mass of the first polymer. Also, we rotate the coordinate system, in such a way, that the z-axis is always pointing towards the other polymer. Fixing the origin to be always at the center of mass of the first polymer changes the diffusion coefficient, $D$, in the Smoluchowski equation to $D'$, with $D' = 2D_p$. $D_p$ is the polymer diffusion coefficient. The rotation of the comoving coordinate system will replace $D'$ with $D'_r$, with $D'_{rr}$ being the radial part of the diagonal element of the diffusion coefficient tensor. To avoid confusion, we use
the symbol $D$ instead of $D'_{rr}$.

The Smoluchowski coagulation process of particles, which is similar to the poly-electrolyte complexation, has adsorbing boundary condition on the surface of the particles. Considering spherical particles with radius $r$, this means that the probability of finding two particles at distance $2r$ is 0 and the particles at this distance adsorb together. For polyelectrolytes this can be interpreted as defining a capture radius, $R_c$, at which the polymers are adsorbed. Simulation studies of Peng and Muthukumar [74] also detected a similar behavior; two oppositely charged polyelectrolytes adsorb into each other almost spontaneously as soon as they reach to a specific distance, $R_c$, which is independent on the initial distance between them. Here, we define an adsorbing boundary condition at $\left| r \right| = R_c$. If we assume a polymer to be equivalent to a spherical particle with radius $R_g$ (see Eqs. (1.5)-(2.8)), the capture radius, $R_c$, can be defined as

$$ R_c = 2R_g. \tag{3.4} $$

Fig. 3.2 shows a schematic of the complexation of two oppositely charged polyelectrolytes. $R_c$ is the cutoff in the radial distance in which two polyelectrolytes at this distance cannot separate from each other. $r_{ij}$ is the distance between the $i$th and $j$th monomers.

The complete process of the complexation can be written as the adsorption and threading. The threading part, involves the release of the counterions to the system and based on the results of the simulation studies of Peng and Muthukumar [74] is much faster than the adsorption part. The adsorption part, however, is more spatially versatile and more sensitive to the physical variables of the system. Here, we only study the adsorption part.
3.2.1 Interaction potential

To solve the Smoluchowski equation, first, we need to find the total interaction potential between the PEs, \( V(r) \), considering the relative position, \( r \), of the second polyelectrolyte. We limit our results to flexible polyelectrolytes. If we adsorb the internal pairwise interactions of each PE to the Kuhn length using the method described in appendix A, we can redefine the PE as a Gaussian chain with the radius of gyration of \( R_g = \sqrt{N\ell\ell_{eff}/6} \) which \( \ell \) and \( \ell_{eff} \) are Kuhn length and effective Kuhn length, with \( N \) the number of Kuhn segments (see Section 2.2 for the details). The density profile for a Gaussian chain is one in which the probability of finding monomers at \( r \) follows a Gaussian distribution around its center of mass. This simplification means the interaction potential, \( V(r) \), has no angular dependence and is only a function of \( r = |r| \). Without loss of generality, we define our comoving system to always rotate in such a way that the center of mass of the second polyelectrolyte is on the \( z \)-axis, so \( r \) does not have any angular parts. Defining subscript \( a \) to refer to the polyelectrolyte which is centered in the comoving coordinate system and \( b \) to the second polymer, the density profile of finding the monomers at \( R \) for each polyelectrolyte, \( \mathcal{P}(R) \), is the integral over the polymer contour which are distributed as a Gaussian chain over their center of mass is

\[
\mathcal{P}_a(R) = \int_0^L ds \delta [R - R_a(s)] = N \left( \frac{3}{2\pi R_g^2} \right)^{3/2} e^{-\frac{3R^2}{2R_g^2}}
\]

\[
\mathcal{P}_b(R) = \int_0^L ds \delta [R - R_b(s)] = N \left( \frac{3}{2\pi R_g^2} \right)^{3/2} e^{-\frac{3|R-R|}{2R_g^2}}
\]

with \( L \) being the total contour length of the polymer, \( L = N\ell \). The interaction potential between polyelectrolytes, \( V(r) \), is sum of the excluded-volume potential, \( V_{ev}(r) \), and the electrostatic potential, \( V_e(r) \), with

\[
V(r) = V_p(r) + V_c(r).
\]
The excluded-volume potential takes the form of the Dirac delta function \[3\]. The total excluded-volume potential of two polymers is

\[
\frac{V_p(r)}{k_B T} = w_{pp} \int_0^L \int_0^L ds_a ds_b \delta [R_a(s) - R_b(s)]
\]

\[
= w_{pp} \int dR \int_0^L ds_a \int_0^L ds_b \delta [R_a(s) - R] \delta [R_b(s) - R]
\]

\[
= w_{pp} \int dR \mathcal{P}_a(R) \mathcal{P}_b(R)
\]

\[
= w_{pp} N^2 \int dR \left( \frac{3}{2\pi R_g^2} \right)^{3/2} e^{-\frac{3R^2}{2R_g^2}} \left( \frac{3}{2\pi R_g^2} \right)^{3/2} e^{-\frac{3|\mathbf{r}|^2}{2R_g^2}}
\]

\[
= w_{pp} N^2 \left( \frac{3}{4\pi R_g^2} \right)^{3/2} e^{-\frac{3|\mathbf{r}|^2}{4R_g^2}}
\]

with

\[
w_{pp} = \frac{l^3}{2} \left( \frac{1}{2} - \chi \right)
\]

and \(\chi\) is the Flory-Huggins parameter. The electrostatic interaction between two monomers is in the form of the Debye-Hückel potential. The total electrostatic potential, \(V_c(r)\), on the first polyelectrolyte due to the second one is

\[
\frac{V_c(r)}{k_B T} = -z_{pB}^2 l_B \int_0^L ds_a \int_0^L ds_b e^{-\kappa |R_a(s) - R_b(s)|}
\]

\[
= -z_{pB}^2 l_B \int dR \int dR' \int_0^L ds_a \int_0^L ds_b e^{-\kappa |\mathbf{R} - \mathbf{R}'|} \frac{|\mathbf{R} - \mathbf{R}'|}{|\mathbf{R} - \mathbf{R}'} \delta [R_a(s) - \mathbf{R}] \delta [R_b(s) - \mathbf{R}']
\]

\[
= -z_{pB}^2 l_B \int dR \int dR' \mathcal{P}_a(R) \mathcal{P}_b(R') e^{-\kappa |\mathbf{R} - \mathbf{R}'|}
\]

\[
= -N^2 z_{pB}^2 l_B \int dR \int dR' \left( \frac{3}{2\pi R_g^2} \right)^{3/2} e^{-\frac{3|R^2 + |\mathbf{r}'|^2|}{2R_g^2}} e^{-\kappa |\mathbf{R} - \mathbf{R}'|}
\]

with \(l_B\) being the Bjerrum length \((l_B = \frac{e^2}{4\pi\epsilon_0\epsilon k_BT})\). In this equation, \(e\), \(\epsilon_0\), and \(\epsilon\) are electron charge, vacuum permittivity, and dielectric constant of the solvent, \(\kappa\) is
the inverse of the Debye length, with \( \kappa^2 = 4\pi l_B c_s \propto c_s \). The above integral can be evaluated analytically. The final form of the electrostatic potential is [78, 79]

\[
\frac{V_c(r)}{k_BT} = \frac{N^2 z_p^2 l_B}{2r} e^{\kappa^2 R_g^2/3} \left[ e^{\kappa r} \text{erfc} \left( \frac{\kappa R_g}{\sqrt{3}} + \frac{\sqrt{3} r}{2R_g} \right) - e^{-\kappa r} \text{erfc} \left( \frac{\kappa R_g}{\sqrt{3}} - \frac{\sqrt{3} r}{2R_g} \right) \right] \tag{3.10}
\]

\( \text{erfc}(x) \) is complimentary error function. Rewriting Eq. (3.10) using scaled complimentary error function, \( \text{erfcx}(x) = \exp(x^2)\text{erfc}(x) \), we get

\[
\frac{V_c(r)}{k_BT} = \frac{N^2 z_p^2 l_B}{2r} e^{-3r^2/4R_g^2} \left[ \text{erfcx} \left( \frac{\kappa R_g}{\sqrt{3}} + \frac{\sqrt{3} r}{2R_g} \right) - \text{erfcx} \left( \frac{\kappa R_g}{\sqrt{3}} - \frac{\sqrt{3} r}{2R_g} \right) \right] \tag{3.11}
\]

Unless otherwise specified, \( N = 100, w_{pp} = 0.01, z_p = 1, \) and \( l_B \approx l \). Fig. 3.3 shows the interaction potential, \( V(r) \) as a function of the distance between two PEs. The red line in Fig. 3.3 denotes the salt concentration of 45 millimoles per liter, \( c_s = 45\text{mM} \). The black line in Fig. 3.3 is for \( c_s = 4\text{mM} \). It is clear that by increasing \( r \), the red line, \( c_s = 45\text{mM} \), approaches 0 much faster than the black line, \( c_s = 45\text{mM} \). The end-point on the right side of both lines represents the capture radius, \( R_c \), with \( R_c = 2R_g \) and \( R_g \).

### 3.3 Results

The probability of finding the center of mass of a polyelectrolyte at position \( \mathbf{r} \) follows the Smoluchowski equation, Eq. (3.2), with \( V(\mathbf{r}) \) being the interaction potential as shown in Eqs. (3.10)-(3.11). Comparing the continuity equation
3.3 Steady-state solution

We start by finding the steady-state solution of the Smoluchowski equation, Eqs. (3.2)-(3.3). The steady-state probability, \( w_s(r) \), is defined as \( \frac{\partial w_s(r)}{\partial t} = 0 \). It can be found by setting the right hand side of Eq. (3.3) to 0.

\[
\nabla \cdot \left[ e^{\frac{V(r)}{k_B T}} \nabla \left( e^{-\frac{V(r)}{k_B T}} w_s(r) \right) \right] = 0. \tag{3.14}
\]

Figure 3.3: Interaction potential for two oppositely charged polyelectrolytes as a function of their center-of-mass distance for 2 different salt concentrations.

\[
\frac{\partial w}{\partial t} - \nabla \cdot J = 0. \tag{3.12}
\]

to Eq. (3.3), allows us to define the flux as

\[
J = -D e^{\frac{V(r)}{k_B T}} \nabla \left( e^{-\frac{V(r)}{k_B T}} w_s(r) \right). \tag{3.13}
\]
We consider the concentration of the second polyelectrolyte at infinity to be constant ($c_p$). The boundary conditions at $r = R_C$ and at $r \to \infty$ are

$$w_s(r)\big|_{r=R_C} = 0 \quad (3.15)$$

and

$$\lim_{r \to \infty} w_s(r) = c_p. \quad (3.16)$$

Using the expression of $\nabla^2$ in spherical coordinate, Eq. (3.14) simplifies to

\[
D \frac{1}{r^2} \frac{\partial}{\partial r} \left[ \frac{V(r)}{r^2 e^{k_BT}} \frac{\partial}{\partial r} \left( e^{-\frac{V(r)}{k_BT}} w_s(r) \right) \right] = 0 \quad (3.17)
\]

\[
r^2 e^{k_BT} \frac{\partial}{\partial r} \left( e^{-\frac{V(r)}{k_BT}} w_s(r) \right) = c_1 \quad (3.17)
\]

\[
\frac{\partial}{\partial r} \left( e^{-\frac{V(r)}{k_BT}} w_s(r) \right) = \frac{c_1}{r^2} e^{-\frac{V(r)}{k_BT}}
\]

\[
e^{-\frac{V(r)}{k_BT}} w_s(r) = c_1 \int_{R_C}^{r} \frac{dr'}{r'^2} e^{-\frac{V(r')}{k_BT}} + c_2
\]

\[
w_s(r) = c_1 \int_{R_C}^{r} \frac{dr'}{r'^2} e^{-\frac{V(r')}{k_BT}} + c_2 e^{\frac{V(r)}{k_BT}}
\]

with $c_1$ and $c_2$ being the constants of the integration and can be calculated from the boundary conditions, Eqs. (3.15)-(3.16).

\[
c_1 = c_p \left[ \int_{R_C}^{\infty} \frac{dr'}{r'^2} e^{-\frac{V(r')}{k_BT}} \right]^{-1} \quad (3.18)
\]

\[
c_2 = 0. \quad (3.19)
\]
We define $c_p = 1$ as the reference for the polymer distribution. Fig. 3.4 shows $w_s(r)$ for three different salt concentrations, $c_s = 4mM$, $c_s = 15mM$, and $c_s = 60mM$. At $r = R_C$, the probability distribution is 0. This probability increases monotonically at $r > R_C$ until it asymptotically reaches 1 at $r \to \infty$. For $r$ close to $R_C$ this probability distribution is approximately a linear function of $r$, which the slope is dependent on the salt concentration, $c_s$. This slope increases by adding salt. Lower salt concentration, means the polyelectrolyte is closer to $R_C$ without getting adsorbed. The limit of $c_s \to \infty$ gives the Debye results of the diffusion-limited coagulation rate in Eq. (3.1) [62].

The capture rate $C$ shows the probability of the complexation process and it the rate at which the polymer adsorbs through the capture surface (at $r = R_C$).
Mathematically, the capture rate defines as the total flux, $J$, reaching the capture surface

$$ C = r^2 e^{-\frac{V(r)}{k_BT}} \frac{\partial}{\partial r} \left( e^{\frac{V(r)}{k_BT}} w_s(r) \right) \bigg|_{r=R_c} $$

(3.20)

with $V(r)$ coming from Eqs. (3.10)-(3.11). Varying the salt concentration will change the effective range of the electrostatic potential. Fig. 3.5 shows the capture rate as a function of salt concentration, $c_s$. Capture rate is very high at lower salt concentrations, $c_s \approx 0$. By increasing salt concentration, the capture rate declines exponentially. This reduction continues until $c_s \approx 10-30 mM$, at which the electrostatic interactions between two polymers becomes almost negligible at $r > R_C$. Through this region, the capture rate still decreases, but it is less sensitive to the $c_s$. Increasing the salt concentration to even higher values cause the electrostatic potential completely diminishes, which causes the capture rate to reach a plateau. The capture rate for this case is equal to the one for neutral polymers and comes from only the stochastic motion of the polymers over the space (this is the case of simple diffusion).

### 3.3.2 Time-dependent solution

After the analytic solution for the steady-state condition, we need to study the time-dependent process of complexation. As we found out from the steady state calculations, at $c_s \approx 10mM$ or more, in the solution of the Smoluchowski equation, Eq. (3.2) or (3.3), the diffusion term dominates. In order to understand the effect of the electrostatic interactions (the drift term), we limit our work to $c_s \approx 0.1-5mM$. Initially, the second polymer is at distance $|\mathbf{r}_0| = r_0$, which gives the initial distribution to be of the form of a delta function

$$ w(\mathbf{r}, 0|\mathbf{r}_0) = \delta(\mathbf{r} - \mathbf{r}_0). $$

(3.21)
Figure 3.5: The capture rate for the steady state as a function of salt concentration, $c_s$.

The probability of finding the polymer at infinity, at any time, is 0, or

$$\lim_{|r| \to \infty} w(r, t| r_0) = 0.$$  \hfill (3.22)

If the two polyelectrolytes are within a constant distance $R_c$, they spontaneously create a polyelectrolyte complex. This means we have adsorbing boundary condition at $|r| = R_c$ and the probability of finding the distance of two polymers to be $r \leq R_c$ is 0.

$$w(|r| = R_c, t| r_0) = 0.$$  \hfill (3.23)

We use the same comoving coordinate system, so only the radial part of the probability distribution will be taken into account,

$$w(r, t| r_0) = w(r, t| r_0) = w(r, t).$$  \hfill (3.24)
We use the Crank-Nicolson method [80], which is a finite difference method for solving partial differential equations, to get \( w(r,t|r_0) \) in the Smoluchowski equation (Eq. (3.2)). \( w(r,t|r_0) \) is the probability of finding the polyelectrolytes to be at distance \( r \), given that their initial distance was \( r_0 \). This probability distribution function is mainly dependent on the salt concentration and the initial distance between the polymers. For the rest of this research, unless it is specifically mentioned, we use \( D^{-1} \) as the unit of the time. For biologically relevant conditions, we consider the salt concentration to be 0.1\( M \) or 100\( mM \). To find the limit of extremely low salt concentration, we consider a second condition for salt concentration with \( c_s = 10^{-4} M = 0.1mM \). Fig. 3.6 shows the evolution of \( w(r,t) \) through time for different salt concentrations and initial distances. The dashed line shows the change in the distance of the center of masses. Fig. 3.6a is for the biophysically relevant condition of \( c_s = 100mM \). We see that the position of center of mass of the polymer (dashed line) is almost unchanged for \( t \approx 0 - 100D^{-1} \). The low salt condition, \( c_s = 0.1mM \), is shown in Fig. 3.6b. Comparing Fig. 3.6a and 3.6b, we see that for the low salt limit, the slope of the dashed line is higher than the one at \( c_s = 100mM \). Also, the time required for the peak value of the probability distribution to reduce by a factor of 2 is about 20\( D^{-1} \) at \( c_s = 100mM \), while it is 5\( D^{-1} \) at \( c_s = 0.1mM \).

The mean distance between the center of masses of polymers \( \langle r \rangle \) is the dashed line in Fig. 3.6. \( \langle r \rangle \) is \( r_0 \) at \( t = 0 \) and changes with time. The mean distance is equal to the first moment of the probability distribution or

\[
\langle r \rangle_t = \frac{1}{N_t} \int_R^\infty d' r' w(r',t)
\]

with

\[ (3.25) \]
\[ N_t = \int_{Rc}^{\infty} dr' w(r', t) \leq 1. \] (3.26)

The contributing factors on the evolution of \( \langle r \rangle \) are the boundary conditions and the interaction potential; In an attractive potential, such as the one here, the drift term reduces the average distance between the polyelectrolytes. However, the diffusion term, can repel the polymers from each other, if their distance is close enough to the capture radius. At \( t \approx 0 \), \( w(r, t) \) is compact and this removes the effect of the diffusion. This means that for any given initial distance and salt concentration, \( \langle r \rangle \) reduces with time. However, after some time, this probability distribution will have a higher variance and the diffusion term starts to contribute to the mean distance.

Fig. 3.7a shows \( \langle r \rangle \) as a function of time for different salt concentrations and initial distances. The \( \lim_{r \to \infty} \langle r \rangle = \langle r \rangle_{\infty} \) does not depend on the initial distance. Fig. 3.7a shows the evolution of the mean distance of the center of masses through time for three different \( r_0 \) at \( c_s = 100mM \). The low salt condition \( c_s = 0.1mM \) is shown in Fig. 3.7b. We see that regardless of the salt concentration, the average distance between the polymers, considering that they have not been adsorbed, rapidly reaches an equilibrium (at \( t < 1 \)). Using this information, we can investigate the effect of the salt concentration on, this equilibrium value, \( \langle r \rangle_{\infty} \). Fig. 3.8 shows the resting mean distance, \( \langle r \rangle_{\infty} \), for different \( c_s \). The relative mean distance \( \langle r \rangle_{\infty}/R_g \) is shown in Fig. 3.8a. The relative mean distance reaches a plateau with increasing the salt concentration. However, the radius of gyration of a polyelectrolyte also changes with salt [3], with prevents the absolute mean distance to reach a plateau. The mean distance \( \langle r \rangle_{\infty} \) is shown in Fig. 3.8b. Increasing the salt concentration reduces the mean distance between the polymers. Addition of salt screens the electrostatic potential and it is not trivial why the mean distance reduces by increasing salt concentration. This
effect comes due to the internal interaction of monomers. Since electrostatic potential reduces by distance, regardless of the salt concentration, the intra-chain interactions are always stronger than the electrostatic interaction between two separated chains.

The mean distance is very different from the rate of the complexation. While the mean distance reaches an equilibrium, the total probability of finding the polymers not being adsorbed reduces monotonically with time. The adsorbing boundary condition at \( R_c \) means that if the polymer reaches this distance, the counterions released in the system dominate the complexation process which cause an almost spontaneous complexation. While the mean distance reaches an equilibrium value, the probability of the polymer getting adsorbed \( d \)

The flux at capture radius gives the rate of this reduction, which is called reaction rate, \( R(t) \). The reaction rate, \( R(t) \), is the total flux (Eq. (3.13)), \( J(r, t) \), of the polyelectrolyte captured at \( R_c \), which after applying spherical symmetry of our comoving system, is

\[
R(t) = -D \int_S d\Omega J(r, t) \\
= 4\pi r_c^2 D \frac{\partial}{\partial r} w(r, t) \bigg|_{r=R_c} \tag{3.27}
\]

where \( S \) denotes the area of a sphere with radius \( R_c \). Fig. 3.9 shows the reaction rate for two different initial distances, \( r_0 = 40nm \) and \( r_0 = 45nm \). For both \( c_s = 0.1mM \) and \( c_s = 100mM \), the reaction rate starts at 0, goes up to a maximum value, and eventually diminishes to 0 at longer time. However, we see that the reaction rate has a take-off time at the beginning. This take-off time is approximately the minimum time that the second PE can reach to the capture radius and increases with initial distance, \( r_0 \). As long as we have not passed this time, we do not see any complexation.
in our system. Fig. 3.9a shows the higher salt limit, $c_s = 100mM$. The effect of the initial distance on take off time is negligible. However, as we can see in Fig. 3.9b, the take off time at low salt limit is highly dependent on the initial distance. Total time of the reaction is dependent on both $r_0$ and $c_s$ and at lower salt concentration, the reaction process is faster.

Using the probability distribution, we can find the half-time, $\tau_{1/2}(r_0, c_s)$. At $t = \tau_{1/2}$, there is a 50% chance that two polymers have been adsorbed into each other and created a polyelectrolyte complex. $\tau_{1/2}$ can be calculated from the probability distribution, $w(r, t)$,

$$\int_{Rc}^{\infty} dr' w(r', t = \tau_{1/2}) = \int_{Rc}^{\infty} dr' w(r', 0) = \frac{1}{2}$$

(3.28)

or from the reaction rate, $R(t)$,

$$\int_{0}^{\tau_{1/2}} dt R(t) = \frac{1}{2}.$$

(3.29)

Fig. 3.10 shows the half-time, $\tau_{1/2}$. Fig. 3.10a shows $\tau_{1/2}$ as a function of the initial distance for $c_s = 100mM$ and $c_s = 0.1mM$. For $r_0/R_g \approx 2 - 5$, we see $\tau_{1/2}$ is proportional to $r_0$. However, the intercept of this linear relation varies with salt concentration. The relation of $\tau_{1/2}$ with salt concentration, $c_s$ is shown in Fig. 3.10b. For the same initial distances, half-time is not linearly dependent on salt concentration and it is almost independent on salt for $c_s \gtrsim 20mM$. If the polymers are initially far enough from each other, increasing $c_s$ from approximately $10 - 20mM$ to $200mM$, can reduce the half time. However, this reduction is negligible compared to $\tau_{1/2}$ itself. This means if polymers concentration is low enough, reducing salt concentration from biophysical range to $c_s \approx 10 - 20mM$ does not change the speed of the complexation.
3.4 Conclusion

We have examined the complexation of oppositely charged polyelectrolytes in an aqueous solution and investigated the complexation process for both steady-state and time-dependent cases. In the steady-state, the probability of the polymer being at capture radius $R_c$ is 0. By going away from the capture distance, this probability increases monotonically and eventually reaches a plateau for larger distances. Increasing the salt concentration will reduce the distance at which this probability reaches a plateau.

To get the kinetics of the complexation, we studied the time-dependent solution of this system. The reaction rate, which defines the rate of complexation process, has an initial take off time which depends on the initial distance between the polymers. At lower salt concentrations, the effect of $r_0$ is more clear in both the duration of the reaction process and the take-off time.

At $t \approx 0$, the position of the center of mass of the polymer is not diffused and the drift term in Smoluchowski equation, Eq. (3.2) decreases the mean distance between the polymers. At first, the diffusion term decreases the certainty of this distance. However, after some time, the diffusion term in Eq. (3.2) equilibrates the mean distance between the polymers. For any physically relevant salt concentration and initial distance, mean distance $\langle r \rangle$ reaches an equilibrium value at $t < D$, which is only dependent on the salt concentration.

The speed of the complexation can be defined by a single parameter $\tau_{1/2}$, which is the half-time of the complexation process. The half-time is dependent on both $r_0$ and $c_s$. If the initial distance of the polymers, for any given salt concentration is $3 - 7R_g$, the half-time changes linearly with $r_0$. While the slope of this linear
relation is almost independent of $c_s$, the intercept is highly dependent on $c_s$. While $\tau_{1/2}$ is linearly dependent on initial distance/ The relation between the half-time and $c_s$ is complicated. At very low salt concentration ($c_s \lesssim 1mM$), half-time is highly dependent on $c_s$ and changes 1-2 orders of magnitude (depending on $r_0$), when $c_s$ changes from $0.1mM$ to $1mM$. Increasing salt concentration from $c_s \approx 1mM$ to approximately $25 - 50mM$ will still increase half-time with $\tau_{1/2} \propto \log(c_s)$. Interestingly, for $c_s \geq 25 - 50mM$, the half-time, $\tau_{1/2}$, is almost independent of salt concentration. This independence is in agreement with the relation of $\langle r \rangle_\infty$ at the same range of $c_s$, as seen in Fig. 3.7.
Figure 3.6: The evolution of the probability distribution, $w(t, r)$ through time as a function of $r$; a) $c_s = 100\text{ mM}$ and the time step of $t = 20D^{-1}$. b) $c_s = 0.1\text{ mM}$ and the time step of $t = 5D^{-1}$. Dashed line shows the value of the average of the probability distribution through time. For both cases, $r_0 = 45$. 
Figure 3.7: The change of the mean distance between the center of masses of the polymers; a) $c_s = 100 \text{mM}$. Red is for $r_0 = 39 \text{nm} (r_0 > \langle r \rangle_\infty)$, blue is for $r_0 = 35 \text{nm} (r_0 \approx \langle r \rangle_\infty)$, and black is for $r_0 = 28 \text{nm} (r_0 > \langle r \rangle_\infty)$; b) $c_s = 0.1 \text{mM}$. Red is for $r_0 = 41 \text{nm} (r_0 > \langle r \rangle_\infty)$ and black is for $r_0 = 36 \text{nm} (r_0 < \langle r \rangle_\infty)$.
Figure 3.8: a) the relative mean distance between the center of masses of the polymers at $t \to \infty$, $\langle r \rangle_\infty / R_g$, as a function of salt concentration; b) the absolute value of the mean distance, $\langle r \rangle_\infty$ for the same range of the salt concentrations.
Figure 3.9: Reaction rate as a function of time: a) $c_s = 100\,mM$; b) $c_s = 0.1\,mM$. In both figures, black is for $r_0 = 45\,nm$ and red is for $r_0 = 40\,nm$. 
Figure 3.10: a) half-time, $\tau_{1/2}$, as a function of initial distance, $r_0$, for different salt concentrations. Black line is for $c_s = 100\,\text{mM}$ and red line is for $c_s = 0.1\,\text{mM}$; b) half-time, $\tau_{1/2}$, as a function of salt concentration, $c_s$. Blue line is for $r_0 = 44\,\text{nm}$, red line is for $r_0 = 40\,\text{nm}$, and black line is for $r_0 = 36\,\text{nm}$.
CHAPTER 4
TRANSLOCATION OF AN INCOMPRESSIBLE VESICLE THROUGH A PORE [1]

4.1 Introduction

The passage of vesicles through a small pore is pertinent to many transdermal applications[81, 82] and drug delivery [81, 83]. While the specifics of the process are quite diverse in terms of chemical details of the various particular systems and the driving forces, the general features have recently been addressed by using statistical mechanical description [84–89]. It is now generally recognized that the fluctuations of the shape of vesicles are controlled by membrane curvature, tension, and interactions with the environment such as colloidal beads [88, 90–99], macromolecules [100], and pores [86, 88, 101]. Coarse-grained parametrization of specific details regarding chemical compositions of the vesicles into universal mechanical features such as bending and stretching has generated considerable insight into the behavior of such intrinsically complex systems. One of the pioneering works using this approach is by Deserno and Gelbart[94], who treated the phenomenon of endocytosis by considering the wrapping of a spherical particle by a vesicle. In this paper, we address the passage of a vesicle through a narrow pore by adopting the same model as that of Deserno and Gelbart[94].

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Basically, the shape fluctuations of a free vesicle are described by a bending modulus $\kappa_c$ and a stretching modulus $\lambda$, with the free energy $F_H$ of the vesicle given by

$$F_H = \frac{1}{2} \kappa_c \oint dA (2H - c_0)^2 + \frac{1}{2A_0} \lambda (A - A_0)^2.$$  \hspace{1cm} (4.1)

The first term on the right-hand side of Eq. (4.1) gives the bending energy in the form of the Helfrich free energy [102] as harmonic in $H$, which is the mean curvature of the membrane for a given vesicle geometry. This is given by $H = \frac{1}{2}(\frac{1}{r_1} + \frac{1}{r_2})$, where $r_1$ and $r_2$ are the principal radii at a point on the surface. The spontaneous curvature $c_0$ is a constant at all points on the vesicle and arises from asymmetry in the areas of the inner and outer surfaces of the lipid bilayer constituting the membrane of the vesicle [102–106]. The integral over the surface area of $(2H - c_0)^2$ gives the energy penalty associated with creating different curvature from the spontaneous curvature[84]. This asymmetry then results in a curvature in the membrane even in the absence of external forces. The energy penalty to bend a vesicle is then with reference to this spontaneous curvature. The integral extends over the whole vesicle surface. The second term on the right-hand side of Eq. (4.1) is the stretching free energy penalty. This is usually taken to be quadratic in the change of the vesicle area $\Delta A = A - A_0$, where $A_0$ is the initial area of the vesicle and $A$ is that of the perturbed vesicle.

The trajectory of a successful translocation of a vesicle from a donor compartment into a receiver compartment through a narrow pore is sketched schematically in Fig. 4.1. The free energy penalty associated with bending and stretching of the vesicle in going from state (a) to state (e) in Fig. 4.1 is expected to result in a free energy barrier for the translocation process [86]. The emergence of free energy barriers for translocation processes is an ubiquitous phenomenon, as seen even for one-dimensional topological structures such as linear polymers [3]. If an external
force sufficiently strong to enable the vesicle to cross the barrier is applied to the vesicle, successful translocation events will occur. The speed of translocation depends on the strength of the applied external force.

The primary goal of the present paper is to assess the dependence of the free energy barrier and the translocation time as functions of the materials parameters $\kappa_c$ and $\lambda$, the strength of the external force which is taken to arise from a pressure gradient, and the feature sizes of the vesicle and pore. The particular details of specific vesicles in terms of their chemical composition and biological contexts are treated only through the materials parameters used in the present coarse-grained model. Here we restrict our calculations to incompressible spherical vesicles of radius $r_0$ (in states (a) and (e) of Fig. 4.1) and cylindrical pores of radius $d$ and length $L$. Following the work
of Deserno and Gelbart [94] and our earlier work [100], we use a simple geometrical ansatz for the vesicle shape and calculate the free energy landscape for vesicle translocation. Based on thus derived free energy profile, we use the Fokker-Planck formalism [100, 107] to compute the translocation rates in terms of the various parameters of the model.

The rest of this chapter is organized as follows: in Section 4.2, we introduce the model and the procedures to calculate the free energy landscape and the translocation time. The main results are discussed in Section 4.3, followed by main conclusions in Section 4.4.

4.2 Model and Calculations

We assume that the vesicle is incompressible with volume $V_0 = 4\pi r_0^3/3$ and that only the area of the vesicle changes during the translocation process through a cylindrical pore of radius $d$ and length $L$. We define the parameter $\beta$ as the ratio of the volume of the pore to that of the vesicle, $\beta = V_p/V_0$, where $V_p = \pi d^2 L$. As sketched in Fig. 4.1, there are three stages of translocation between the initial state (Fig. 4.1a) and the final state (Fig. 4.1e): (i) pore-filling stage, (ii) crossing stage, and (iii) pore-depletion stage. In order to describe the whole passage of the vesicle from the donor compartment to the receiver compartment, we define the translocation coordinate as $\alpha = V_t/V_0$, where $V_t$ is the volume of the vesicle that is either inside the pore or that has passed through the pore. During the pore-filling stage, $V_t$ is the same as the volume of the vesicle inside the pore ($0 < \alpha < \beta$). During the crossing stage, the translocation coordinate represents the volume of the vesicle that is depleted from the donor compartment. When the vesicle is completely deleted from the donor compartment, $\alpha = 1$. Then onwards, the depletion of the vesicle from the pore begins. For complete translocation, the vesicle must be fully transferred out of the pore. During
the pore-depletion stage, $V_t$ is the sum of the volume of the vesicle in the receiver compartment and the total volume of the pore. Therefore, we extend the domain of the translocation coordinate $\alpha$ (defined above as the fraction of the volume of the vesicle that is removed from the donor compartment) beyond 1 to $1 + \beta$ for the full translocation event. If the length of the pore is zero, this extended domain for the translocation coordinate is unnecessary.

We follow the procedure of Deserno and Gelbart [94] and Mirigian and Muthukumar [100] to calculate the free energy penalty associated with bending and stretching of the vesicle that accompany the translocation coordinate. When an additional curvature is demanded on the vesicle at the pore entrance (and at the pore exit), we introduce a torus at the contact point between the vesicle and pore mouth as illustrated in Fig. 4.2. To begin with, the free energy of the isolated vesicle in the initial state is given by Eq. (4.1) as

$$F_{0b} = \frac{\kappa c}{2} \left[ 4\pi r_0^2 \left( \frac{2}{r_0} - c_0^2 \right) \right] = \frac{\kappa c}{2} \left[ 4\pi \left( 2 - r_0 c_0^2 \right) \right] \quad (4.2)$$

$$F_{0s} = 0$$

where $F_{0b}$ and $F_{0s}$ denote the bending and stretching contributions, respectively. This is also the result in the final state of translocation (Fig. 4.1e). The free energy landscape for the three stages of translocation is derived next.

### 4.2.1 Filling stage

As shown in Fig. 4.2a, the additional curvature of the vesicle at the pore entrance or exit is obtained by introducing a torus at the contact point between the vesicle and the pore boundaries. This geometrical construction is made to generate smooth curvature variation along the translocation process. There are four components joined together in this state. First, we have a partial spherical shape, that is like a full
Figure 4.2: Various parameters used to define the free energy of the deformed vesicle. (a) Filling stage: $r$ is the radius of the partial sphere, $b$ is the small radius of the toroidal vesicle. Dotted lines show the cross-section of a hypothetical torus that keeps the curvature of the vesicle to be smooth. $\theta$ is the angle between the center of the spherical part and center of the small toroidal ring. (b) Crossing stage: Two toroids are needed. $b', r'$ and $\theta'$ correspond to the toroid on the receiver side, and $b, r,$ and $\theta$ correspond to the donor side as in (a).

sphere with a missing angle $\theta$. Next, there is a toroidal part that connects the sphere part to the pore. The third component is a cylinder with radius $d$ and length $l < L$. Finally, we have a hemisphere with radius $d$.

We define three parameters on the sphere-toroid part and $l$ as the length of the pore that is filled by vesicle. Radius of partial sphere is $r$ which is smaller than $r_0$. Inner and outer radii of the torus are respectively $d$ and $d + 2b$ with the angle between the line connecting the center of torus (pore) to the center of sphere and the one from the center of the sphere and circular part of toroid is $\theta$ (see Fig. 4.2a). Change of the curvature should be continuous through the connecting point of toroid and sphere.

This gives us a relation between $r$, $\theta$, and $b$

$$\sin \theta = \frac{b + d}{r + b}$$

$$b = \frac{r \sin \theta - d}{1 - \sin \theta}.$$
Since the vesicle is incompressible, volume of the vesicle inside the pore is $\alpha V_0$ and the volume of the vesicle in the donor compartment is $V_{\text{donor}} = (1 - \alpha)V_0$. The first definition gives us a relation for $l$

$$\pi d^2 l + \frac{2}{3} \pi d^3 = \alpha V_0 = \frac{4}{3} \pi \alpha r_0^3$$

$$l = \frac{2}{3} d \left( 2 \alpha r_0^3 \frac{d}{d^3} - 1 \right).$$

The second condition gives us a constraint. We can find the total volume as a function of $r$, and $\theta$, for any value of $\alpha$ by using Eq. (4.3). Geometrical consideration gives the volume to be equal to volume of a sphere with a missing angle $\theta$ plus a conical shape with radius at the bottom of the cone as $r + b$, and angle $\theta$, and subtracting volume of partial toroid with inner radius $b$, and outer radius $d + 2b$, between angles $\frac{1}{2}\pi + \theta$ and $\pi$. Each part is independently calculated in the supporting information.

The expression for the volume of the vesicle in the donor compartment is

$$V_{\text{donor}} = (1 - \alpha)V_0 = V_{I,sph} + V_{I,\text{cone}} - V_{I,\text{tor}}$$

$$= \left[ \frac{2}{3} \pi r^3 (1 + \cos \theta) \right] + \left[ \frac{1}{3} \pi (b + d)^3 \cot \theta \right]$$

$$- \left[ \pi [(b + d) b^2 \left( \frac{\pi}{2} - \theta \right) - \frac{2}{3} b^3 \cos \theta] \right]$$

with $b$ defined in Eq. (4.3). Solution to this equation gives $r(\theta)$ and we use the result in writing the free energy for each given $\alpha$. After that, we minimize the free energy with respect to $\theta$. 

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Next we calculate the bending free energy term in the Helfrich free energy Eq. (4.1)

\[ F_{I,bending} = F_{I,b,sph} + F_{I,b,tor} + F_{I,b,cyl} + F_{I,b,hem}. \] (4.6)

Using supporting information, the first term is

\[
F_{I,b,sph} = \frac{1}{2} \kappa_c \int dA (2 \frac{1}{r} - c_0)^2
= \frac{1}{2} \kappa_c 2\pi r^2 (2 \frac{1}{r} - c_0)^2
= \frac{1}{2} \kappa_c 2\pi (2 - c_0 r)^2 (1 + \cos \theta).
\] (4.7)

The second term is

\[
F_{I,b,tor} = \frac{1}{2} \kappa_c \left[ -2\pi (c_0 b + 2)^2 \cos(\theta) + 2\pi c_0 (c_0 b + 2) \left( \frac{\pi}{2} - \theta \right) (b + d) 
+ \frac{2\pi (b + d)^2}{b \sqrt{d} \sqrt{2b + d}} \left\{ \pi - 2 \tan^{-1} \left( \frac{\sqrt{d}}{\sqrt{2b + d}} \tan \left[ \frac{1}{2} \left( \theta + \frac{\pi}{2} \right) \right] \right) \right\} \right].
\] (4.8)

The next two terms in Eq. (4.6) are easy to find as

\[
F_{I,b,cyl} = \frac{1}{2} \kappa_c \pi d^2 l \left( \frac{1}{d} - c_0 \right)^2
= \frac{1}{2} \kappa_c \frac{2}{3} \pi \left( 2\alpha \frac{r_0^3}{d^3} - 1 \right) (1 - c_0 d)^2
\] (4.9)

\[
F_{I,b,hem} = \frac{1}{2} \kappa_c 2\pi d^2 \left( \frac{1}{d} - c_0 \right)^2
= \frac{1}{2} \kappa_c 2\pi (2 - c_0 d)^2.
\] (4.10)
To calculate the stretching free energy term in the Helfrich free energy, Eq. (4.1), we need to find the change in the total area,

$$\Delta A_I = A_I - A_0$$  \hspace{1cm} (4.11)

$$= A_{I,sph} + A_{I,tor} + A_{I,cyl} + A_{I,hem} - A_0$$

$$= 2\pi r^2 (1 + \cos \theta) + 2\pi b \left[ \left( b + d \right) \left( \frac{\pi}{2} - \theta \right) - b \cos \theta \right]$$

$$+ 2\pi d^2 \left( 4\alpha r_0^3 - \frac{2}{3} \right) + 2\pi d^2 - \left[ 4\pi r_0^2 \right].$$

Therefore the second term in Eq. (4.1) is

$$F_{I,\text{stretching}} = \frac{1}{2A_0} \lambda (\Delta A_I)^2,$$  \hspace{1cm} (4.12)

where $A_0 = 4\pi r_0^2$ and $\Delta A_I$ is defined in Eq. (4.11).

### 4.2.2 Crossing stage

This stage corresponds to the state where the vesicle is on both sides of the pore (See Fig. 4.1b) with $\beta < \alpha < 1$ ($\beta = V_p/V_0$). The calculation is similar to the filling stage, but we have similar conditions for the receiver compartment side as well. We define new primed parameters which refer to the receiver side ($r', b'$, and $\theta'$). While $b$ is defined in Eq. (4.3), $b'$ is

$$\sin \theta' = \frac{b' + d}{r' + b'}$$  \hspace{1cm} (4.13)

$$b' = \frac{r' \sin \theta' - d}{1 - \sin \theta'}$$

Also, we have two separate conditions corresponding to the donor and receiver sides,

$$V_{\text{donor}} = (1 - \alpha)V_0 = V_{sph} + V_{cone} - V_{tor}$$  \hspace{1cm} (4.14)

$$V_{\text{receiver}} = (1 - \alpha')V_0 = V'_{sph} + V'_{cone} - V'_{tor}$$
with \((1 - \alpha) + (1 - \alpha') + \beta = 1\), or \(\alpha' = 1 + \beta - \alpha\). Similar to the filling stage, these give us \(r\) and \(r'\) as functions of \(\theta\) and \(\theta'\), respectively.

The bending energy in this stage is in the form

\[
F_{III,\text{bending}} = F_{III,b,sph} + F_{III,b,tor} + F'_{III,b,sph} + F'_{III,b,tor}. \tag{4.15}
\]

\(F_{III,b,sph}\) and \(F_{III,b,tor}\) are defined in Eqs. (4.10)-(4.8). Also \(F'_{III,b,sph}\) and \(F'_{III,b,tor}\) are similar with substitutions \(x \rightarrow x' (x \equiv r, b, \theta)\). \(F_{III,b,pore}\) is

\[
F_{III,b,pore} = \frac{1}{2} \kappa_c 2\pi L d (\frac{1}{d} - c_0)^2 - \frac{1}{2} \kappa_c 2\pi \beta \frac{4 r_0^3}{3 d^3} (1 - c_0 d)^2 \tag{4.16}
\]

with \(L\) being the total pore length and \(\beta\) being volume of pore divided by the volume of vesicle.

Calculation of area is also similar to that for the filling stage with the addition of terms from the receiver side

\[
\Delta A_{III} = A_{III} - A_0 \tag{4.17}
\]

\[= A_{III,sph} + A_{III,tor} + A_{III,pore} + A'_{III,sph} + A'_{III,tor} - A_0 \]

\[= \left[ 2\pi r^2 (1 + \cos \theta) \right] + \left[ 2\pi b \left[ (b + d) \left( \frac{\pi}{2} - \theta \right) - b \cos \theta \right] \right] \]

\[+ \left[ 2\pi r'^2 (1 + \cos \theta') \right] + \left[ 2\pi b' \left[ (b' + d) \left( \frac{\pi}{2} - \theta' \right) - b' \cos \theta' \right] \right] \]

\[+ \left[ 2\pi \beta \frac{4 r_0^3}{3 d^3} \right] - \left[ 4\pi r_0^2 \right] \]

and

\[
F_{III,\text{stretching}} = \frac{1}{2 A_0} \lambda (\Delta A_{III})^2. \tag{4.18}
\]
4.2.3 Depletion stage

This is exactly analogous to the filling stage with the substitution of $x$ by $x'$ ($x \equiv r, b, \theta$). Therefore, the result for this stage is given by Eqs. (4.6)-(4.18) by replacing $r, b,$ and $\theta$ by $r', b'$, and $\theta'$, respectively.

4.2.4 External driving force

In the absence of any external driving force, the free energy landscape is symmetric between the donor and receiver compartments, separated by a barrier as shown in Section 4.3 (Fig.4.3). In order for the vesicle to undergo a net successful translocation from the donor compartment to the receiver compartment, the free energy of the system after translocation must be lower than that before translocation. This downhill free energy landscape is provided by an externally imposed driving force. The nature of the driving force depends on the specifics of the system. One example is the use of an externally imposed electric field to push charged vesicles or charged microgels through pores. An analogous situation arises for translocation of charged polymers such as DNA and proteins through nanopores[3]. By repeating the procedures outlined in Ref.[3], it is in principle possible to derive the free energy contribution from such an externally imposed electric field on a vesicle bearing surface charges. The electrostatics of curved vesicle-fluid interfaces inside the pore is also quite complicated. We do not address the translocation of charged vesicles in this paper. Another example of the external force to drive the vesicle from the donor compartment to the receiver compartment is using a pressure gradient, as considered in an analogous problem by Linke et al.[88]. By maintaining a higher pressure in the donor compartment relative to the receiver compartment, the vesicle is pushed into the receiver compartment. The mechanics of elastic surfaces is very complex and in particular at the vesicle-fluid interface when a vesicle is partially filled inside a pore across a pressure gradient. Nevertheless, the essential physics is that when an incompressible
vesicle of volume $V_0$ is pressed by an external pressure $P_1$ in the donor compartment into the receiver compartment with pressure $P_2$ through an orifice, the free energy changes from $P_1V_0$ to $P_2V_0$. Since $P_1 > P_2$, the free energy landscape is downhill. The elastic distortion associated with the intermediate states of translocation, resulting in the barrier between the initial and final states, is treated as above. For pores of finite length, there is an additional friction between the vesicle and the pore wall, which is ignored. Therefore, the zeroth-order model of pressure-driven external contribution to free energy is

$$F_{ext} = P(V_0 - V_t)$$

(4.19)

where $V_t$ is the volume of the incompressible vesicle that is depleted from the donor compartment and $P_1 = P$ with $P_2 = 0$. An equivalent form for the external free energy has previously been used by Linke et al.[88], where $P$ is taken as the osmotic energy difference between the donor and receiver compartments. Since the starting free energy value in constructing the free energy landscape is taken as zero, the constant $PV_0$ is absorbed in defining the reference state so that

$$\Delta F_{ext} = -PV_t.$$  

(4.20)

Using the definition of $\alpha = V_t/V_0$ and multiplying and dividing by the constant $1 + \beta$, where $\beta = V_p/V_0$, the above equation is rewritten as

$$\Delta F_{ext} = -f_0\frac{\alpha}{1 + \beta} \quad 0 < \alpha < 1$$

(4.21)

where $f_0$ is the energy term $PV_0(1 + \beta)$. We take the above equation for $0 < \alpha < 1$. At $\alpha = 1$, the vesicle is completely depleted from the donor compartment. From now on, for the rest of the translocation process, we take $\Delta F_{ext} = -f_0/(1 + \beta)$.  

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Adding this term to the Helfrich free energy, we get the total free energy of the system as
\[ F = F_H + F_{\text{ext}} = F_{\text{bending}} + F_{\text{stretching}} + \Delta F_{\text{ext}} \]  \hspace{1cm} (4.22)
for each of the three stages described above.

### 4.2.5 Kinetics of translocation

Now that we have free energy landscape as a function of the translocation coordinate \( \alpha \), we follow the procedure of the Fokker-Planck formalism given in Ref. [100] and obtain the mean translocation time as the mean first passage time given by
\[
\tau = \frac{1}{k_0} \int_0^{1+\beta} d\alpha_1 \int_0^{\alpha_1} d\alpha_2 e^{\frac{F(\alpha_1) - F(\alpha_2)}{k_B T}}.
\]  \hspace{1cm} (4.23)

In using this equation, we have assumed that the translocation time is longer than the relaxation time for the vesicle to relax from any distortion from its equilibrium state, by invoking the standard detailed balance arguments behind the Fokker-Planck formalism. Furthermore, we have solved the corresponding equation for the time-dependent probability distribution with the absorption boundary condition at the pore exit facing the receiver compartment and the reflecting boundary condition at the pore entrance facing the donor compartment. This set of boundary conditions is chosen for the present problem where there is a pressure driving the vesicle from the donor compartment to the receiver compartment. In the above equation, \( k_0 \) is a parameter representing local friction of a surface element of the vesicle as it goes through the pore and this is taken to set the unit of time for the problem. \( k_0 \) is a microscopic and non-universal parameter. The other parameters in the calculation are \( \frac{T_0}{d} \), \( \lambda \), \( \kappa_c \), \( c_0 \), \( f_0 \), and \( \beta \). In the present paper, we report the results mainly for \( c_0 = 0 \) and \( \beta = 0.3 \) as illustrative examples. We define the unit of energy as \( k_B T \) and \( d \) is the unit of length. We use values for the rest of the parameters from different experiments [108–110]. We have taken \( \kappa_c \approx 2 – 5 \), \( \lambda \approx 1 – 10 \), \( r_0/d \approx 1.5 – 3 \), \( d = 1 \),
and $f_0$ is defined in such a way that total translocation time will be between $10$ and $10^5$ in units of $k_0^{-1}$. The results given in the following section for these values of the parameters can readily be extended to other values of the parameters appearing in the free energy expressions.

4.3 Results and Discussion

4.3.1 Translocation Barrier

Representative results for the free energy profile as a function of the translocation coordinate $\alpha$ in the absence of any external driving potential difference are given in Fig. 4.3. To calculate the free energy at any given $\alpha$, we first find $r$ as a function of $\theta$ from the cubic root of the volume constraint, Eq. (4.5). Only one of the roots satisfies the conditions $0 < \theta < \pi/2$ and $d < r < r_0$. Substituting $r(\theta)$ in the Helfrich free energy, Eq. (4.1), we obtain the free energy as a function of $\theta$. Next, we minimize this free energy with respect to $\theta$ for the values of $\sin^{-1}(d/r_0) < \theta < \pi/2$ ($\sin \theta$ cannot be smaller than pore radius divided by initial radius of the sphere). We consider values of $\alpha$ from 0 to $1 + \beta$ at increments $\delta = 0.01$. Finally, we get the free energy landscape of the system by shifting the free energy by a constant so that the initial free energy is 0. Here the radius of the initial vesicle is 2.5 times the pore radius, the bending modulus is $2k_BT$, and the stretching modulus is $5k_BT$ per square of the pore radius. We have presented the results in Fig. 3 with and without spontaneous curvature. The three stages of translocation are also marked on the figure. In general, there is a free energy barrier for the translocation process. The presence of spontaneous curvature reduces the barrier, the effect being larger in the crossing stage. Naturally, the free energy landscape is symmetric in $\alpha$, as there is no driving potential difference between the initial and final states for Fig. 4.3.
Figure 4.3: Helfrich free energy for $r_0 = 2.5d$, $\beta = 0.3$, $\kappa_c = 2$ and $\lambda = 5$. Solid line (black) is without spontaneous curvature. Dashed (blue) is with existence of $c_0$. The three stages of translocation are also marked.

The role of the externally imposed potential difference is illustrated in Fig. 4.4 for the same parameters as in Fig. 4.3, when there is no spontaneous curvature. We follow the same method to numerically calculate the free energy as described above for $f_0 = 0$. For the driving potential difference $f_0 = 30$, the barrier height is decreased from $28k_BT$ to $14k_BT$ for $\kappa_c = 2$. A change of the stretching modulus parameter $\lambda$ from 5 to 2.5 does not affect the barrier significantly. However, if the bending modulus is decreased by a factor of two, the barrier essentially goes away.

4.3.2 Translocation Time

Using Eq. (4.23), the translocation time is calculated for various combinations of values of the parameters. The effect of the external driving potential difference $f_0$ on $\tau$ is given in Fig. 4.5 for systems with different elastic moduli and two different vesicle
sizes. To calculate the double integral in Eq. (4.23), we sum over numerical values of free energy that we calculated in the previous section for any given value of $\alpha$ and multiply it by the increment value, $\delta$ (i.e. replacing $\int_0^{1+\beta} d\alpha$ with $\delta \sum_i F(\alpha = i\delta)$). For systems with the same surface characteristics (same elastic moduli), acceptable range for $f_0$ (to get a translocation time between $10^{-10^5}$) is highly dependent on vesicle radius, $r_0$. For example, in the case with $\kappa_c = 3$, $\lambda = 5$, in order to get a translocation time of 500, we need the driving potential difference, $f_0$, to be approximately 15, if $r_0 = 1.75$. However, only increasing vesicle radius to $r_0 = 2.5$ will increase the driving potential difference to $f_0 = 70$, in order to get the same translocation time. As is evident from the structure of the equations for the translocation time and the free energy expression, the translocation time should be roughly exponential with the negative of the driving potential difference when the barrier is insignificant. This is

Figure 4.4: Free energy in the presence of external field for $r_0 = 2.5d, \beta = 0.3$. Red (dotted) is for $\kappa_c = 1$ and $\lambda = 5$. Blue (dashed) is for $\kappa_c = 2$ and $\lambda = 2.5$. Black (solid) is for $\kappa_c = 2$ and $\lambda = 5$.

$c_0 = 0$ and $f_0 = 30$. 

exactly what is seen in Fig. 4.5 for the various combinations of $\kappa_c$ and $\lambda$, for each vesicle radius.

The effects of elastic moduli on the translocation time are illustrated in Fig. 4.6. In Fig. 4.6a, the dependence of $\tau$ on the bending modulus $\kappa_c$ is given for two different vesicle radii and two different driving potential differences, by keeping the stretching modulus parameter $\lambda$ as a constant at $\lambda = 4$. By keeping $f_0$ constant, increasing $\kappa_c$ by a factor of 2 will increase $\tau$ up to 6 orders of magnitude. On the other hand, the effect of $\lambda$ on $\tau$ is weaker, as shown in Fig. 4.6b. While the translocation time, $\tau$, increases exponentially with $\kappa_c$ and $\lambda$, we see that the effect of $\lambda$ is much weaker in comparison to changes in the bending modulus, $\kappa_c$. Although $\log \tau$ is roughly proportional to both elastic moduli ($\kappa_c$ and $\lambda$), the slope of this law is highly dependent on the vesicle radius, $r_0$, and the external potential difference, $f_0$.

Finally, we show the effect of the vesicle radius on the translocation time. We find that $\tau$ depends on $r_0$ roughly as the exponential of $r_0^2$, as shown in Fig. 4.7. The linear fit to the numerically calculated results is included in this figure. Here $\kappa_c = 1$, $\lambda = 3$, and $f_0 = 43$. The result of $\log \tau$ being proportional to $r_0^2$ arises from the fact that both the bending and stretching free energies are proportional to the surface area, $r_0^2$. As has already been pointed out through Fig. 4.5, the ratio of the vesicle radius to the pore radius plays a crucial role in controlling the translocation time.

4.4 IV. Conclusions

We have derived a formula for the translocation time of an incompressible spherical vesicle driven through a narrow pore under an externally applied potential difference in terms of the bending and elastic moduli of the vesicle and its radius, and the radius and length of the pore. In this formulation, we have treated the deformation
Figure 4.5: Effect of driving force for different values of $\kappa_c$ and $\lambda$. (a) $r_0 = 1.75$. (b) $r_0 = 2.5$.

of the vesicle by the pore within the Helfrich free energy formalism and a constant driving potential difference. The free energy landscape is calculated by considering
Figure 4.6: Effect of elastic moduli for different vesicle sizes with appropriate external forces: (a) translocation time as a function of $\kappa_c$; by keeping $f_0$ constant, increasing $\kappa_c$ by a factor of 2 will increase $\tau$ up to 6 order of magnitude. (b) translocation time as a function of $\lambda$; changing $\lambda$ from 2 to 10 will change $\tau$ almost two orders of magnitude.
the three stages of translocation, namely pore-filling, crossing, and pore-depletion stages. Using thus derived free energy landscape for the translocation process, we have implemented the Fokker-Planck formalism to obtain the average translocation time as the mean first passage time.

In general, there is a free energy barrier for translocation of the vesicle through a narrow pore arising from the obligatory elastic deformation of the vesicle. In the absence of the driving potential difference, the barrier is symmetric in the translocation coordinate and its magnitude depends on the various parameters of the system. For example, the barrier decreases as the spontaneous curvature increases. The free energy barrier is mitigated by the presence of an externally applied potential difference and the translocation time becomes shorter as the strength of the driving potential difference is increased. The average translocation time depends roughly exponentially
on the negative of the driving potential difference. Also, an approximate exponential
dependence of the average translocation time on the bending modulus and stretching
modulus parameter is observed, although the effect from the bending modulus is very
drastic in comparison to that of the stretching modulus. A change in the vesicle
size has the biggest effect on the translocation time. The average translocation time
depends on the vesicle radius $r_0$ as $\exp(r_0^2)$.

Indeed, the model presented here is a zeroth-order model in comparison to the bi-
ological systems which possess very rich chemical features. In our model, the specific
chemical details of the vesicles are parametrized in terms of the materials param-
ters in an effort to extract the universal large scale properties associated with the
translocation of a single vesicle through a narrow pore. It is hoped that the above
predicted dependencies of translocation kinetics on the elastic properties and size of
the vesicle and on the driving potential difference would stimulate experiments on
model vesicular systems.
CHAPTER 5
EFFECTS OF LONG-RANGE INTERACTIONS ON CURVATURE ENERGIES OF VIRAL SHELLS [2]

5.1 Introduction

It has recently become clear that long-range interactions are extremely important also in the self-assembly of capsid proteins into viral shells and that they determine the self-assembly phase diagram [111]. Electrostatic interactions that originate in the effective charge on the capsid proteins [9], as governed by the pH and the ionic strength of the bathing solution, can fundamentally change the phase diagram of the capsid protein of the cowpea chlorotic mottle virus (CCMV) yielding single-wall and multi-wall capsids, as well as tubes and free protein [112]. These results seem to implicate that a change in the spontaneous curvature of the capsid as a function of the charge asymmetry of the proteinaceous shell as well as the solution conditions regulates the size of the shell [113, 114]. We thus focus our attention on precisely how, in the context of empty capsid shells, the long-range electrostatic and van der Waals (vdW) interactions together conspire to modulate the mesoscopic properties of spheroidal aggregates, specifically their spontaneous curvature.

Standard principles of colloid and nanoscale stability theory in fact identify *grosso modo* two types of interactions that together govern the self-assembly and disassembly of biological macromolecules and their molecular aggregates [115]: the electrostatic interactions depending on the specific nature of molecular charges [116]

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and the ubiquitous vdW interactions depending on the dielectric response properties of molecular material [117, 118]. This is also the most fundamental assertion of the DLVO (Deryaguin-Landau-Verwey-Overbeek) theory of macromolecular stability [104]. When macromolecular aggregates are net charged, the ensuing (screened) Coulomb interactions between identical molecules are usually repulsive, with solvent effects due to hydrophilic moieties contributing an additional short-range component to the overall molecular repulsions [119]. On the other hand, neutral molecular aggregates usually interact via non-specific vdW attractions [120], augmented again by the solvent effects engendered by the hydrophobic moieties along the solvent-exposed surfaces [121]. In fact, in the context of proteins, the interactions are mostly entropy-driven [122, 123], usually interpreted to originate in the water-mediated hydrophobic interactions. As part of the vdW interactions, the s.c. zero frequency term, is also entropic in origin, it is with some difficulty that one can differentiate between this part of vdW interactions and the hydrophobic interactions proper [124, 125]. Of these four interactions hydrophobic and/or hydration forces correspond to an effective interaction arising from the statistical properties of water molecules around the dissolved macromolecular moieties, while the electrostatic and vdW forces are indeed "true" forces that act even in the absence of any solvent. The overall stability condition then proceeds from comparing the strengths of these interactions.

The important thing to notice is that a stable state of matter is possible only if other forces apart from electrostatic ones are present, as implied by the Earnshaw theorem for classical theory of electrostatic interactions. In addition vdW forces by themselves are also unable to stabilize matter, at least for bodies with permittivities that are all higher or lower than that of the intervening medium. Only by combining the two together, or more unusually having bodies with alternating higher/lower permeabilities than the intervening medium, can full stability of matter be achieved.
This is also the most fundamental assertion of the DLVO (Deryaguin-Landau-Verwey-Overbeek) theory of macromolecular stability.

Since the bathing solution in the biological milieu contains various dissolved ionic species the electrostatic interaction depends on its exact composition [126], i.e. the concentration and valency of salt ions, due to Debye-Hückel screening, but also on the amount of charge they carry that can be modified by shifting the dissociation equilibrium via the solution pH [127, 128]. At the same time the vDW interaction is a complicated functional of the dielectric response function of the components of the macromolecular aggregates [117] as well as of the bathing solvent, that can be modified by solutes, e.g., low molecular weight solutes such as glucose and sucrose [129].

While there are obvious similarities, there are nevertheless fundamental differences between elasticity of rigid proteinaceous shells of tethered capsomeres [130] and spheroidal lipid vesicles that are composed of a quasi 2D fluid layer of lipid molecules [131]. The electrolytes on the two sides of an impermeable membrane can in principle differ, an assumption usually unrealistic for viral shells that are typically completely permeable to various ionic species (however, see Ref. [132]). The contribution of electrostatic interactions to spontaneous curvature as well as bending rigidity renormalization of lipid membranes was standardly analyzed within the mean-field Poisson-Boltzmann (PB) framework starting from the seminal work of Winterhalter and Helfrich [133, 134] and later generalized to more realistic scenarios [135–140]. In what follows we will also delimit ourselves to monovalent electrolytes described on the level of the mean-field PB theory. Though the effects of multivalent electrolytes have been standardly studied on the PB level [139], they cannot in general be analyzed within the mean-field framework [127] and lead to instabilities which have no counter-
part in the behavior of the monovalent salts [141]. Contribution of vdW interactions to spontaneous curvature and bending rigidity renormalization of lipid membranes have also been extensively analyzed on a variety of levels starting with the Lifshitz theory of vdW interactions based approach of Parsegian and Weiss [142] and later generalized on different levels [143–149].

The main differences between the 2D fluid layer of soft lipid molecules and crystal-like assemblies of tethered capsomers boil down to the fact, that the latter are usually permeable to salt ions (even to larger ones), being in thermodynamic equilibrium with the bulk reservoir that sets the ions’ chemical potential. The effective surface charge density of capsomers can thus be viewed as highly constrained and as not responding to small curvature deformations. These specific features of proteinaceous shells lead to important differences and make the available theoretical results valid for lipid layers in general not applicable. We will consider spherical shells only and calculate the contribution of vdW interactions to spontaneous curvature on the level of the Lifshitz theory for general asymmetric layers and at the same time use the linearized PB theory to evaluate also the contribution of asymmetric charged shells with fixed surface charge density. This will allow us to derive the full DLVO expression for the change in the spontaneous curvature while assuming a known experimentally determined value for the bending rigidity. In this way, we bypass the unknown position of the ”neutral surface” that actually changes the exact renormalization of the bending rigidity only (see 5.2).

In what follows we will be interested in the stability properties of the macromolecular aggregates, as described by the bending elastic modulus and the spontaneous radius of curvature, of the already formed equilibrium structures such as spheroidal lipid vesicles on the one hand, and proteinaceous hard icosahedral empty virus shells
on the other. While these two systems are rather dissimilar, the first one being composed of a quasi 2D fluid layer of lipid molecules, while the second one can be modelled as a crystal-like assembly of tethered capsomeres, they can nevertheless be described by the same model of a thin charged shell of dielectric material, immersed into an aqueous solution. This allows us to investigate rather generally the stability properties of these macromolecular aggregates as they depend on the changes in ionic strength or pH, but also on more subtle changes of the dielectric response function of the bathing solution.

5.2 Theory

5.2.1 Curvature expansion of the free energy

We analyze a thin spheroidal charged shell and expand its vdW - Lifshitz interaction free energy as well as its electrostatic free energy in terms of the reciprocal radius of curvature $R$. The total interaction free energy of the spheroidal shell can be written as

$$F = \int_S dS \left( \sigma_0 + \frac{a}{R} + \frac{b}{R^2} + \ldots \right),$$

(5.1)

where $S$ is the area of the shell, $dS$ is its element and $\sigma_0$, $a$ and $b$ are constants that depend on the details of the long-range interactions. This expansion should be compared with the mesoscopic elastic deformation free energy [150]

$$F = \int_S dS \left( \sigma + \frac{1}{2}K_c \left( \frac{1}{R} - \frac{1}{R_0} \right)^2 + \ldots \right),$$

(5.2)

where $\sigma$ is the surface tension, $K_c$ is the bending rigidity and $R_0$ is the spontaneous radius of curvature, allowing us to identify the interaction renormalization of the mesoscopic bending rigidity and spontaneous radius of curvature as

$$\sigma \rightarrow \sigma_0 + \frac{K_c}{R_0^2}, \quad K_c \rightarrow K_c + 2b, \quad \frac{1}{R_0} \rightarrow \frac{1}{R_0} - \frac{a}{K_c}.$$  

(5.3)
All the mesoscopic parameters of shell elasticity thus contain a bare part, due to short range interactions that is not taken into account specifically, and a renormalized long-range DLVO interactions part, just as in the case of semi-flexible polyelectrolytes [151]. While the electrostatic renormalization of mesoscopic elasticity parameters has been analyzed on various levels of sophistication (see above), the complete DLVO assessment of elastic parameter renormalization has not been properly addressed.

It is obvious from expansion Eq. (5.1) that depending on how we define the origin for the radius of curvature, or by making the substitution $R \rightarrow R + \delta R$, part of the $a$ coefficient can migrate into the $b$ coefficient and thus the renormalization of the bending rigidity depends on the details of the deformation process, i.e., what part of the layer remain unaffected by the deformation and what is the exact position of this "neutral surface". In order to avoid this ambiguity in the definition of the bending rigidity renormalization, we will concentrate purely on the spontaneous curvature and the surface tension, taking the bending rigidity as an empirical parameter. Similar indeterminacy has been noted also in the context of membrane electrostatics [139], where the results on the bending rigidity renormalization depend on the details of the deformation process. We will derive the first two terms of the curvature expansions of both, the vdW interactions on the level of the macroscopic Lifshitz theory, as well as the electrostatic interactions on the level of the Debye-Hückel theory. As will become obvious, both of them can be derived in an explicit analytic form suitable for relevant numerical computations.
5.2.2 Curvature expansion of the vdW-Lifshitz interaction

The Lifshitz theory of vdW interactions connects the dielectric response function at imaginary frequencies, $\varepsilon(i\zeta)$, defined via the imaginary part of the dielectric response function $\varepsilon''(\omega)$, as [152]

$$
\varepsilon(i\zeta) = 1 + \frac{2}{\pi} \int_0^\infty \frac{\omega \varepsilon''(\omega)}{\omega^2 + \zeta^2} d\omega,
$$  \hspace{1cm} (5.4)

with the interaction free energy between the materials described by this dielectric response [117]. The connection is via the fluctuation-dissipation theorem and the Lifshitz theory actually evaluates the free energy contribution of all the electromagnetic field fluctuations. We will consider the vdW interactions across a curved parallel single layer system that will mimic a thin spherical curved molecular sheet. In the derivation of the curvature expansion we modify the original methods of Weiss, Parsegian and Witte [142, 145] based on the Lifshitz theory.

The vdW free energy of this system depends on the dielectric mismatch $\Delta(i\zeta)$ at the inner and outer boundaries of the thin spherical sheet of inner radius $R$ and thickness $w \ll R$, i.e.,

$$
\begin{align*}
\Delta_{32}(i\zeta) &= \frac{\varepsilon_3(i\zeta) - \varepsilon_2(i\zeta)}{\varepsilon_3(i\zeta) + \varepsilon_2(i\zeta)}, \\
\Delta_{21}(i\zeta) &= \frac{\varepsilon_2(i\zeta) - \varepsilon_1(i\zeta)}{\varepsilon_2(i\zeta) + \varepsilon_1(i\zeta)}. 
\end{align*}
$$  \hspace{1cm} (5.5)

Here, by assumption, the dielectric response of the shell is that of the capsid proteins, $\varepsilon_2(i\zeta) = \varepsilon_p(i\zeta)$, and $\varepsilon_3(i\zeta) = \varepsilon_1(i\zeta) = \varepsilon_w(i\zeta)$ is the dielectric response of the aqueous solvent. Dielectric response functions at imaginary frequencies $\varepsilon_k(i\zeta)$ are obtained from a Kramers-Kronig transform of the imaginary part of the dielectric function in a standard way [117], once one either chooses a model for the frequency response or
measures it directly for a particular material. While the frequency response of capsid proteins is presently not (yet) available, it exists for many other materials [120]. It is obvious that for any value of the argument as well as any model one should have $-1 < \Delta_{ij}(i\zeta) < 1$. Usually the imaginary frequency dependence of $\epsilon_k(i\zeta)$ can be approximated as

$$\epsilon_k(i\zeta) = 1 + \sum_j \frac{d_j}{1 + \zeta \tau_j} + \sum_j \frac{f_j}{\omega_j^2 + g_j \zeta + \zeta^2},$$  \hspace{1cm} (5.6)$$

where all the constants are material specific and can be obtained from standard references.

In the Lifshitz theory of vdW interactions the free energy for a single spherical parallel layer system can be calculated in a closed form as a sum over the log of the secular determinant, $D(\omega, \mathbf{k}; g)$, whose zeros on the real frequency, $\omega$-axis yield the wave-vector $\mathbf{k}$ dependent frequencies of the eigenmodes of the Maxwell’s equation in the chosen interaction geometry as a function of the parameters describing that geometry $g$ [117]. The vdW interaction free energy can then be derived in the general form

$$G_{vdW} \equiv \sum_{N=0}^{\infty} \sum_{\mathbf{k}} \log (D(i\zeta_N, \mathbf{k}; g)),$$  \hspace{1cm} (5.7)$$

where the sums are over the geometry dependent set of wave-vectors $\mathbf{k}$ and over the thermal Matsubara frequencies, $\zeta_N = 2\pi N k_BT/\hbar$, where $N$ is an integer, $k_BT$ and $\hbar$ are the thermal energy and the Planck’s constant. The $N = 0$ term is counted with a weight $1/2$ indicated by the prime in the sum. The Matsubara sum, embodying the finite temperature effects, is trivial and can be done numerically for a chosen model of the frequency dependence of the dielectric response function.
For a single spherical parallel layer system, of thickness $w$ and inner shell radius $R$, this general formula is reduced to [142, 145]

$$G_{vdW}(R, w, \Delta_{32}, \Delta_{21}) = \sum_{N=0}^{\infty} G_{N}(R, w, \Delta_{32}(i\zeta_N), \Delta_{21}(i\zeta_N)),$$  \hspace{1cm} (5.8)

where we have defined the single Matsubara frequency free energy function

$$G_{N}(R, w, \Delta_{32}(i\zeta), \Delta_{21}(i\zeta)) = k_B T \sum_{\ell=0}^{\infty} (2\ell + 1) \ln \left[ 1 + \frac{4\ell(\ell+1)\Delta_{32}\Delta_{21}(1 + \frac{w}{R})^{-(2\ell+1)}}{(2\ell + 1 + \Delta_{32})(2\ell + 1 + \Delta_{21})} \right]$$

$$= \sum_{\ell=0}^{\infty} G^{(\ell)}(R, w; N),$$  \hspace{1cm} (5.10)

that can be obtained from the solutions of the Maxwell’s equations in the spherical shell geometry [142, 145]. The only remaining "wave-vector" in the sum Eq. (5.7) is then the degree $\ell$ of the spherical harmonic function.

Since what we want is an expansion in curvature up to the second order, Eq. (5.1), we will only consider terms in the above free energy up to that order. In what follows we will analyze the $R$ and $w$ dependence of $G_{N}(R, w, \Delta_{32}(i\zeta), \Delta_{21}(i\zeta))$ by modifying the previous method [145]. Using Euler-Maclaurin summation formula

$$\sum_{l=0}^{\infty} f(l) = \int_{0}^{\infty} dx f(x) - \frac{1}{2}[f(\infty) - f(0)]$$

$$+ \frac{1}{12} [f'(\infty) - f'(0)] - \frac{1}{720} [f'''(\infty) - f'''(0)] + ..., $$

we transform Eq. (5.8) into
\[
\sum_{\ell=0}^{\infty} G^{(\ell)}(R, w; N) = \int_0^\infty d\ell \ G^{(\ell)}(R, w; N) - \frac{1}{12} G''(0)(R, w; N) + \ldots, \quad (5.12)
\]

where the other terms are either zero or do not contribute to the order \( R^{-2} \). We next introduce the variable \( l = xR/w \) and keep terms to the second order, i.e., to \((w/R)^2\), as assumed in our curvature expansion Eq. (5.1). This yields the following expansion for the surface free energy density

\[
\frac{1}{4\pi R^2} G_{vdW}(R, w, \Delta_{32}, \Delta_{21}) = k_B T \sum_{N=0}^{\infty} \left[ F_0 (\Delta^*, \bar{\Delta}; w) + \frac{1}{R} F_1 (\Delta^*, \bar{\Delta}; w) \right. \\
+ \left. \frac{1}{R^2} \left( F_2 (\Delta^*, \bar{\Delta}) + \tilde{F}_2 (\Delta^*, \bar{\Delta}; w) \right) \right] \quad (5.13)
\]

with the definitions

\[
F_0 (\Delta^*, \bar{\Delta}; w) = \frac{1}{2\pi w^2} \int_0^\infty dx \ x \ln \left( 1 + \Delta^* e^{-2x} \right) = -\frac{1}{8\pi w^2} Li_3(\Delta^*) \quad (5.14)
\]

\[
F_1 (\Delta^*, \bar{\Delta}; w) = \frac{1}{4\pi w} \left[ \int_0^\infty dx \ln \left( 1 + \Delta^* e^{-2x} \right) \right. \\
+ \left. \int_0^\infty dx \frac{\Delta^* e^{-2x}}{1 + \Delta^* e^{-2x}} (x^2 - x - \bar{\Delta}) \right] \\
= \frac{1}{4\pi w} \tilde{F}_1 (\Delta^*, \bar{\Delta}) \quad (5.15)
\]
\[ F_2 (\Delta^*, \overline{\Delta}) = \frac{1}{24\pi} \int_0^\infty dx \frac{\Delta^* e^{-2x}}{(1 + \Delta^* e^{-2x})^2} \left[ (6x^3 - 20x^2 + 6x(3 - \overline{\Delta}) - 6(1 - \overline{\Delta})) - \Delta^* e^{-2x} \left( 8x^2 - 12x + 6 \right) \right] - \frac{\Delta^*}{12\pi (1 + \Delta + \Delta^*)} \]

and

\[ \tilde{F}_2 (\Delta^*, \overline{\Delta}; w) = -\frac{1}{48\pi} \int_0^\infty dx \frac{\Delta^* e^{-2x}}{x (1 + \Delta^* e^{-2x})^2} \left[ 6 \left( 1 + \Delta^* - \overline{\Delta}^2 \right) + \Delta^* e^{-2x} \left( 6 + 6\Delta^* - 3\overline{\Delta}^2 \right) \right] \]

\[ \simeq \frac{\Delta^* \left( 6 \left( 1 + \Delta^* - \overline{\Delta}^2 \right) + \Delta^* \left( 6 + 6\Delta^* - 3\overline{\Delta}^2 \right) \right)}{48\pi (1 + \Delta^*)^2} \log \frac{w}{a}, \]

where

\[ \overline{\Delta} = \Delta_{32} + \Delta_{21} = \Delta_{wp} + \Delta_{pw} \]

\[ \Delta^* = \Delta_{32} \Delta_{21} = \Delta_{wp} \Delta_{pw}. \]

\[ \tilde{f}_1 (\Delta^*, \overline{\Delta}) \text{ is} \]

\[ \tilde{f}_1 (\Delta^*, \overline{\Delta}) = 4\pi \Delta^* \left[ \frac{1}{2} \Phi(-\Delta^*, 2, 1) + \frac{2}{3} \Phi(-\Delta^*, 3, 1) - \frac{1}{2^2} \Phi(-\Delta^*, 2, 1) - \frac{\overline{\Delta}}{2} \Phi(-\Delta^*, 1, 1) \right]. \]

which is independent of \( w \).

This is now the final expression for the vdW free energy expansion in terms of the inverse radius. All the integrals in the above expression can in fact be calculated explicitly and analytically via the Lerch function, see Appendix A. The implied
Matsubara summation can finally be taken for any concrete model of the dielectric response. The lowest order term, containing the integral of $F_0(\Delta^*, \bar{\Delta}; w)$, is identical to the vdW free energy of interaction between semi-infinite media ”1” and ”3” across the plane-parallel slab of medium ”2”, scaling as the inverse second power of the thickness of the slab, $w$ [117].

The logarithmic divergence of $\tilde{F}_2(\Delta^*, \bar{\Delta}; w)$ is consistent with the previous results on the renormalization of the bending rigidity to the lowest order in the dielectric mismatch [143], while formula Eq. (5.17) presents the full Lifshitz result to all orders in the dielectric mismatch. Of the three terms in Eq. (5.13), we will concentrate only on the first two. The first pertains to the renormalization of the surface free energy where its bare value, stemming from short range interactions between the capsid proteins is unknown, while the third term, describing the bending rigidity renormalization, allows for an ambiguity because - depending on the definition of the ”neutral surface” - it contains an undefined constant. We thus take the full, renormalized value of the bending rigidity as an empirical constant.

5.2.3 Curvature expansion of the electrostatic interaction

The PB theory of electrostatic interactions sets the framework for calculation of the curvature expansion of the electrostatic part of the free energy [116]. In the model considered, based on the rigid nature of the proteinaceous virus shell, we assume a fixed surface charge density at the inner and at the outer boundary of the shell, which can nevertheless differ [9]. We also assume a different static dielectric permittivity for the shell then for the bathing aqueous solution in which the shell is immersed, following closely the approach of Ref. [153]. Again we will delimit ourselves to the surface tension and the spontaneous curvature term for the same reasons as already
invoked in the context of the vdW interaction.

We start with the work of Duplantier who considered three cases, two of them of interest to us: in the first case, the membrane is charged with density $\sigma_0$, and the surface is transparent, i.e. the boundary condition at the surface is

$$\left. \partial_r \phi_{in} \right|_{r=R^-} - \left. \partial_r \phi_{out} \right|_{r=R^+} = \frac{\sigma_0}{\varepsilon \varepsilon_0},$$

(5.20)

In the second case, the membrane is opaque and screens out the interior from the exterior. In this case, the boundary conditions are separated,

$$\left. \partial_r \phi_{in/out} \right|_{r=R^\pm} = \frac{\sigma_{\pm}}{\varepsilon \varepsilon_0}.$$

(5.21)

In the case of a transparent membrane, $r_0' = \pi \sigma_0^2 / \kappa \varepsilon \varepsilon_0$, $a = 0$, and $b = -c = 1/2$. For a sphere where the radii of curvature are equal, it can be thus seen that the terms in $1/(\kappa R)^2$ vanish. Additionally, from the exact solution we know there are no higher order terms.

Even though the opaque membrane is not interesting to us since the separation of interior and exterior is not feasible, there are two different conclusions in that case concerning the free energy expansion. The second order terms are present, in contrast to the transparent membrane, and if the electrolyte is asymmetric, i.e. $\kappa_{in} \neq \kappa_{out}$, then also the first order (linear) term is non-zero, $a \neq 0$. For our interests here the pertinent problem is a capsid as two charged shells with distinct surface charge densities.
The inner radius of a charged shell is again taken as $R$, with surface charge density $\sigma_1$, and the outer of radius $R + w$, with surface charge density $\sigma_2$. Both can be extracted from a detailed statistical analysis of the VIPERdb for different virus families [154]. The majority of analyzed viruses tend to have a slightly negative $\sigma_2$. The charge on the inner shell is however less universal and most of the analyzed viruses have either negative or positive $\sigma_1$. This conclusion has to be amended if one adds disordered N-tails of the proteins on the inner surface that shift the inner shell charge to more positive values (for details see Ref. [154]) strongly influencing also the stable length of the encapsidated genome [12].

We are seeking again an expansion of the free energy up to the second order in terms of the inverse powers of the inner radius of curvature $R$, assuming again that $w \ll R$. The static dielectric constant of water is $\varepsilon_w$, and that of the of the capsid protein $\varepsilon_p < \varepsilon_w$ are taken as $\varepsilon_p = 5$ and $\varepsilon_w = 80$. Additionally, we denote $\mu = \varepsilon_p / \varepsilon_w < 1$.

In what follows we delimit ourselves exclusively to the linearized PB (Debye-Hückel, DH) theory within its range of validity [116]. The electrostatic part of the free energy is then given as a functional of the mean-field electrostatic potential, $\varphi(r)$, in the form

$$
G_{el} = \frac{1}{2} \varepsilon_w \varepsilon_0 \int_{(V)} \left( (\nabla \varphi(r))^2 + \kappa^2 \varphi(r)^2 \right) d^3 r = \varepsilon_w \varepsilon_0 \int_{(S=\partial V)} \varphi(r_S) \left( n \cdot \nabla \varphi(r_S) \right) d^2 r_S.
$$

(5.22)

$\kappa$ is the inverse Debye screening length set by the ionic strength of the monovalent salt of concentration $c_0$ in the regions $r < R$ and $r > R + w$, i.e., $\kappa^2 = 2 \beta e^2 c_0 / (\varepsilon_0 \varepsilon_w)$ and is the same inside and outside the shell, whereas within the shell $\kappa \equiv 0$. For a spherical shell of thickness $w$ and inner radius $R$, the mean-field electrostatic potential
by assumption depends only on the radial coordinate, $\varphi(r) = \varphi(r)$, and satisfies either the DH equation or the Laplace equation

$$\nabla^2 \varphi(r) = \kappa^2 \varphi(r), \text{ or } \nabla^2 \varphi(r) = 0 \text{ for } R \leq r \leq R + w. \quad (5.23)$$

These two equations have to be solved with appropriate boundary conditions, i.e. $\varepsilon_w \varepsilon_0 \partial_r \varphi(r = R)$ has a jump equal to $\sigma_1$ and at $\varepsilon_w \varepsilon_0 \partial_r \varphi(r = R + w)$ a jump equal to $\sigma_2$. The overall form of the mean-field electrostatic potential on $r$ is very similar to the one displayed on Fig. 5 of Ref. [153].

While one could formally extend the PB theory to multivalent salts [139] the results could not be properly validated on the mean-field level [126] and lead to additional considerations that will not be addressed here [141]. Furthermore, we work exclusively in the grand canonical ensemble where the screening parameters of the electrolyte are set by the bulk reservoir, a straightforward consequence of the fact that the viral capsids are usually completely permeable to salt as opposed to lipid vesicles where the number of the salt ions in the interior can be constrained [139].

Within the limit of the DH theory for spherically symmetric shells, the electrostatic free energy Eq. (5.22) for a charged shell of thickness $w$ as defined above, can be rewritten as [137]

$$G_{el} = \varepsilon_w \varepsilon_0 \oint_{(S = \partial V)} \varphi(r_S) (n \cdot \nabla \varphi(r_S)) d^2 r_S \quad (5.24)$$

$$= \frac{1}{2} 4\pi R^2 \sigma_1 \varphi(R) + \frac{1}{2} 4\pi (R + w)^2 \sigma_2 \varphi(R+w),$$

where the mean-field electrostatic potential can be obtained from the solutions of the DH equation outside the proteinaceous layer, and from the Laplace equation.
inside, Eq. (5.23), since the proteinaceous shell itself is impenetrable to ions, with
the boundary conditions specified above. The general solution of this problem can be
obtained analytically but we will only use the expansion in terms of $R$ to the second
order.

The final form of the free energy Eq. (5.24) for this particular geometry can then
be derived as

$$G_{el} = \frac{2\pi R^2}{\kappa \varepsilon_0 \varepsilon w} \left( \frac{M}{L} + \frac{N}{L} \right), \quad (5.25)$$

where the general forms of $M$, $N$, and $L$ are derived in Ref. [153] and are related to
the electrostatic potential at the two boundaries.

To the second order in $1/\rho = 1/(\kappa R)$ we can simplify the general expressions for
the electrostatic potential and after some algebra obtain the following form of the
three terms in the inverse curvature expansion

$$L = (2\mu + (\kappa w)) \times \left( 1 + \frac{(\kappa w)}{\rho} + \frac{(\kappa w)^2}{\rho^2} \left[ \frac{((\kappa w) + 1)(\mu - 1)}{(\kappa w)(2\mu + (\kappa w))} \right] \right), \quad (5.26)$$

$$M = \left( \mu(\sigma_1 + \sigma_2) + (\kappa w)\sigma_1 \right) + \frac{\rho}{\kappa w} \left[ ((\kappa w) + 1)\sigma_1 + 2\mu\sigma_2 \right] + \frac{(\kappa w)^2}{\rho^2} \mu \sigma_2, \quad (5.27)$$

and

$$N = \left( \mu(\sigma_1 + \sigma_2) + (\kappa w)\sigma_2 \right) + \frac{\rho}{\kappa w} \left( 2\mu\sigma_1 + (4\mu + 3(\kappa w) - 1)\sigma_2 \right) \quad (5.28)$$

$$+ \frac{(\kappa w)^2}{\rho^2} \left( \mu\sigma_1 + 3(2\mu + (\kappa w) - 1)\sigma_2 \right).$$
In fact the only place where the curvature expansion needed to be taken into account is in the last expression, \( N \); everything else being exact. This allows us to derive the final expression for the curvature expansion of the electrostatic part of the surface free energy density as

\[
\frac{1}{4\pi R^2} \mathcal{G}_{el}(\sigma_1, \sigma_2, \kappa, w) = \frac{1}{2\kappa \varepsilon_0 \varepsilon w} \left( f_0(\sigma_1, \sigma_2, \kappa, w) + \frac{f_1(\sigma_1, \sigma_2, \kappa, w)}{\kappa R} \right) \\
+ \frac{f_2(\sigma_1, \sigma_2, \kappa, w)}{(\kappa R)^2},
\]  

where we introduced the shorthand

\[
f_0(\sigma_1, \sigma_2, \kappa, w) = \frac{\mu (\sigma_1 + \sigma_2)^2 + (\kappa w)(\sigma_1^2 + \sigma_2^2)}{2\mu + (\kappa w)},
\]

(5.30)

\[
f_1(\sigma_1, \sigma_2, \kappa, w) = (\kappa w) \left( \frac{(3\mu + 2(\kappa w) - 1)\sigma_2^2 + 2\mu \sigma_1 \sigma_2 - (\mu - 1)\sigma_1^2}{2\mu + (\kappa w)} \right),
\]

(5.31)

and

\[
f_2(\sigma_1, \sigma_2, \kappa, w) = \frac{\kappa w}{(2\mu + (\kappa w))^2} \left( (\mu - 1) [(\kappa w)(\mu - 1) - \mu] \sigma_1^2 \\
- 2\mu((\kappa w) + 1)(\mu - 1)\sigma_1 \sigma_2 \\
+ \left[ (\kappa w)^3 + (\kappa w)^2(4\mu - 1) + (\kappa w)(5\mu^2 - 4\mu + 1) - \mu(\mu - 1) \right] \sigma_2^2 \right).
\]

(5.32)

In general the above free energy density is not symmetric in the two surface charge densities that were assumed to be constant during the deformation. As already stated
this seems a reasonable assumption in the context of the rigid proteinaceous shells but can not be invoked in the context of symmetric lipid vesicles [139]. In the latter case the lipid membrane is to a good approximation impermeable to water as well as to hydrated ions and thus represents an impermeable barrier that decouples the two compartments, a situation very much opposite to the case of a porous proteinaceous capsid.

In the limit of vanishing thickness \( w \to 0 \) we then obtain straightforwardly

\[
\lim_{w \to 0} G_{el}(\sigma_1, \sigma_2, \kappa, w) = \pi (\sigma_1 + \sigma_2)^2 R^2 / \kappa \varepsilon \varepsilon_0,
\]

which is the correct expression for a single shell of radius \( R \) and surface charge \( \sigma_0 = \sigma_1 + \sigma_2 \). This corresponds to the dielectrically transparent case of Duplantier [138], considered before. Perhaps more interesting is the fact that the higher order terms are asymmetric in terms of \( \sigma_1 \) and \( \sigma_2 \). Our analysis takes fully into account the coupling between the inner and the outer layer of the proteinaceous shell and we made no approximation to decouple the two [155].

5.2.4 Combining the electrostatic and vdW interactions

We can now write down the curvature expansion for the total free energy. Adding Eq. (5.13) and Eq. (5.29) will give us the terms in the free energy expansion: \( R^0 \), \( R^{-1} \), and \( R^{-2} \). This total surface free energy density then leads to the following interaction renormalization of the surface tension, spontaneous radius of curvature and the mesoscopic bending rigidity can be written succinctly as

\[
\frac{1}{4\pi R^2} F_{\text{tot}} = k_B T \sum_{N=0}^{\infty} \left( F_0 (\Delta^*, \overline{\Delta}; w) + \frac{F_1 (\Delta^*, \overline{\Delta}; w)}{R} + \frac{F_2 (\Delta^*, \overline{\Delta}; w)}{R^2} \right) + \frac{1}{2\kappa \varepsilon \varepsilon_0} \left( f_0 (\sigma_1, \sigma_2, \kappa, w) + \frac{f_1 (\sigma_1, \sigma_2, \kappa, w)}{\kappa R} + \frac{f_2 (\sigma_1, \sigma_2, \kappa, w)}{(\kappa R)^2} \right). \tag{5.33}
\]
From here and from the identification of the renormalized mesoscopic elasticity parameters in Eq. 5.3 it follows that

$$\sigma \rightarrow \sigma_0 + \frac{K_c}{R_0^2} + k_B T \sum_{N=0}^{\infty} F_0 (\Delta^*, \Delta; w) + \frac{1}{2\kappa \varepsilon_0 \varepsilon_w} f_0 (\sigma_1, \sigma_2, \kappa, w)$$

(5.34)

$$\frac{1}{R_0} \rightarrow \frac{1}{R_0} + \frac{1}{2K_c} \left( k_B T \sum_{N=0}^{\infty} F_1 (\Delta^*, \Delta; w) + \frac{1}{2\kappa^2 \varepsilon_0 \varepsilon_w} f_1 (\sigma_1, \sigma_2, \kappa, w) \right).$$

(5.35)

$$K_c \rightarrow K_c + \frac{1}{2K_c} \left( k_B T \sum_{N=0}^{\infty} F_2 (\Delta^*, \Delta; w) + \frac{1}{2\kappa^3 \varepsilon_0 \varepsilon_w} f_2 (\sigma_1, \sigma_2, \kappa, w) \right).$$

(5.36)

Though we wrote down the full result for the surface energy, spontaneous curvature, and bending rigidity renormalization, we will specifically investigate only the contribution of vdW and electrostatic interactions to the surface tension and spontaneous curvature of the spheroidal shell, Eq. (5.35), treating the bending rigidity as a phenomenological parameter derived from experiment. As already stated, the exact form of the interaction renormalized bending rigidity depends crucially on the assumed position of the "neutral surface" pending on the nature of the model one assumes for the shell. To avoid this ambiguity, we consider the value of the bending rigidity as an input phenomenological parameter.
5.3 Numerical results

The spontaneous curvature interaction renormalization depends on several parameters and we will investigate specifically the dependence on the capsid charge $\sigma_1$ and the charge asymmetry $r = \sigma_1/\sigma_2$ between the inner and outer surface, the thickness $w$, the ionic strength of the bathing solution and the dielectric response of all the media involved. The latter in fact represents the biggest challenge, as the dielectric response of capsid proteins in the optical and UV regime of frequencies, that contributes most to the vdW interactions, is simply not known because the unavailable details of the electronic structure of large capsid proteins (W.-Y. Ching, personal communication and Ref. [156]).

The variation of the charge ratio $r$ can be seen as a proxy for the pH dependence of both surface charge densities in a more complete theory of virus shell electrostatic, that would consistently include also charge regulation of the capsid proteins [128, 157, 158]. Charge regulation refers to the details of the protonation/deprotonation equilibria at the dissociable sites of the capsid proteins amino acids as formalized in the seminal work of Ninham and Parsegian [124, 125] and formulated within the Poisson-Boltzmann (PB) theory of electrostatic interactions [116]. In this theory the charges are not assumed to be fixed but respond to pH and salt concentration changes.

While some partial dielectric data for bovine serum albumin (BSA) do exist and were used by Roth et al. [159] to calculate the Hamaker coefficient of protein-protein vdw interactions, no full spectral data for capsid proteins are available [120]. We thus approximate the frequency dependent dielectric response of capsid proteins, $\varepsilon_p(i\zeta)$, by that of hydrocarbons with four ultraviolet relaxation frequencies (for details see Ref. [117]). Without detailed capsid protein spectral data this is the best thing we
can do. For the numerical computations we then use the standard forms for the frequency dependent dielectric response of water, $\varepsilon_w(i\zeta)$, described with one microwave relaxation frequency, five infrared relaxation frequencies, and six ultraviolet relaxation frequencies [160].

The additive renormalization of the surface tension and spontaneous curvature can then be cast into the form

$$\sigma \rightarrow \sigma_0 + \frac{K_c}{R_0^2} + \frac{k_BT}{2\pi w^2} \left( \mathcal{H} + \frac{1}{(\kappa\ell_B)} \left( \frac{w}{\ell_{GC}} \right)^2 \left[ \frac{\varepsilon_p}{\varepsilon_w} (r+1)^2 + (\kappa w)(r^2+1) \right] \right)$$

(5.37)

$$\frac{1}{R_0} \rightarrow \frac{1}{R_0} + \frac{(k_BT/K_c)}{8\pi w} \left( \mathcal{H'} + \frac{2}{(\kappa\ell_B)} \left( \frac{w}{\ell_{GC}} \right)^2 \times \left[ \frac{(3\varepsilon_p \varepsilon_w + 2(\kappa w) - 1) + 2\varepsilon_p r - (\varepsilon_p - 1)r^2}{2\varepsilon_p \varepsilon_w + (\kappa w)} \right] \right)$$

(5.38)

Above we introduced the Gouy-Chapman length pertaining to the outer surface charge density $\sigma_2$ as $\ell_{GC} = 1/(2\pi\ell_B(\sigma_2/\varepsilon_0))$ and the Bjerrum length $\ell_B = \varepsilon_0^2/(4\pi\varepsilon \varepsilon_0 \ k_B T)$, with $r = \sigma_1/\sigma_2$. Numerically the Bjerrum length in water equals 0.74 nm. The above form of the additive renormalization of the spontaneous curvature has a minimal value at $r_{min} = \varepsilon_p/(\varepsilon_p - \varepsilon_w)$, whereas the renormalized surface tension is monotonic in $r$. These are the final expressions for the surface tension and spontaneous curvature renormalization.
Two "Hamaker coefficients" pertaining to the zeroth and first order curvature expansion, $\mathcal{H}$ and $\mathcal{H}'$, are obtained by assuming a symmetric configuration, where water is on both sides of the proteinaceous shell, i.e.

\[
\mathcal{H} = \sum_{N=0}^{\infty} \int_0^{\infty} dx \ x \ln \left( 1 - \Delta_{wp}(i\zeta_N)^2 e^{-2x} \right) \\
= -\frac{1}{4} \sum_{N=0}^{\infty} Li_3 \left( -\Delta_{wp}(i\zeta_N)^2 \right)
\]

\[
\mathcal{H}' = \sum_{N=0}^{\infty} \tilde{f}_1 \ (\Delta_{wp}(i\zeta_N)\Delta_{pw}(i\zeta_N), \Delta_{wp}(i\zeta_N) + \Delta_{pw}(i\zeta_N)) \\
= \sum_{N=0}^{\infty} \left[ \int_0^{\infty} dx \ln \left( 1 - \Delta_{wp}(i\zeta_N)^2 e^{-2x} \right) \\
- \int_0^{\infty} dx \ \frac{\Delta_{wp}(i\zeta_N)^2 e^{-2x}}{1 - \Delta_{wp}(i\zeta_N)^2 e^{-2x}} \left( x^2 - x \right) \right]
\]

With the standard water dielectric spectra [160] and hydrocarbon spectra [117] taking the place of the unknown protein dielectric spectra, this yields $\mathcal{H} \simeq -0.177$ and $\mathcal{H}' \simeq -0.386$, where the Matsubara summation included the first 500 terms.

Empty viral capsids tend to have at least slightly negative outer shell [154]. There is more diversity concerning the charge on the inner shell which can be negatively or positively charged. The inclusion of disordered N-tails of the capsid proteins into the charge statistics noticeably shifts the inner shell charge towards more positive values. This is especially relevant in the case of ssRNA viruses, where the disordered N-tails contribute significantly to the strongly positively charged interior, and where the charge is correlated with the genome length due to the non-specific electrostatic
interactions acting as an assembly mechanism [12, 161, 162].

In addition, models of multishell capsids in the presence of N-tails have highlighted the importance of charged tails in determining the capsid size, which can in the multishell conformations differ from the capsid’s preferred (spontaneous) radius of curvature, due to the interplay of electrostatic repulsion between the tails and attraction between the tails and the outer surface of the neighboring shell [163]. While we simply assign the contribution of the N-tails to the inner surface charge density $\sigma_2$ in order to keep our model consistent, we thus consider the possibility that $\sigma_2$ has either negative or positive sign, the latter stemming from the contribution of the positively charged tails to the inner charge.

The inner and outer surface charge density of the virus capsids is in general quite large when compared with other charged biomolecules, being in the range $[-0.4, 0.4] \ e_0/\text{nm}^2$. Invoking the previously obtained average capsid radii this implies net charge values in the range $\sim 4500 \ e_0$ [164]. The exact values of the surface charge density depend on the charge model, i.e., single- vs. double-shell models, and on the presence of the charged N-tails as discussed above (for details see Ref. [164]). We thus introduce the charge asymmetry parameter as the ratio of inner and outer surface charge as $r = \sigma_1/\sigma_2$ and in the following consider the range $r \in [-1, 1]$.

According to the above statistics of virus charges the Gouy-Chapman length corresponding to $0.4 \ e_0/\text{nm}^2$ is $\ell_{GC} = 0.54 \ \text{nm}$, while the outer-inner charge ratio spans $-1 < r < 1$. For more than 75% of viruses analyzed in Ref. [154], the thickness is confined to a narrow range, $w \simeq 1.5 - 4.5 \ \text{nm}$, with $w \simeq 3 \ \text{nm}$ as a good estimate of the average. The monovalent salt concentration can be taken in the typical range $0.001 - 1 \ \text{M}$, which amounts to Debye lengths of $10.75 - 0.34 \ \text{nm}$.  

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In order to understand the consequences of spontaneous curvature renormalization we rewrite Eq. (5.37), (5.38) in the form that contains only the interaction-renormalized part

$$
\sigma = \frac{k_B T}{w^2} \tilde{\sigma} \quad \text{with} \quad \tilde{\sigma} = \frac{\mathcal{F}_0\left(\left(\frac{\kappa B}{\ell}, \frac{w}{\ell_{GC}}, \kappa w, r\right)\right)}{2\pi \left(\frac{\kappa B}{\ell}\right)^2 \left(\frac{\kappa B}{\ell_{GC}}\right)^2} (5.41)
$$

$$
\frac{1}{R_0} = \left(\frac{k_B T}{K_c}\right) \frac{1}{w} \frac{1}{\tilde{R}_0} \quad \text{with} \quad \frac{1}{\tilde{R}_0} = \frac{\mathcal{F}_1\left(\left(\frac{\kappa B}{\ell}, \frac{w}{\ell_{GC}}, \kappa w, r\right)\right)}{8\pi \left(\frac{\kappa B}{\ell}\right)^2 \left(\frac{\kappa B}{\ell_{GC}}\right)^2} (5.42)
$$

where $\tilde{\sigma}$ and $\tilde{R}_0$ are now dimensionless contributions to the surface tension and spontaneous curvature due to DLVO interactions. The surface tension and spontaneous curvature obviously have the scale of $k_B T/w^2$ and $(k_B T/K_c)/w$, respectively. For the former it amounts to a fraction of the surface tension of water ($\sim 0.5-4 \text{ pN/nm}$) and for the latter within the range of the capsid radii ($10 - 100 \text{ nm}$), obtained from the estimated values of capsid elasticity [164]. $\mathcal{F}_{0,1}\left(\left(\frac{\kappa B}{\ell}, \frac{w}{\ell_{GC}}, \kappa w, r\right)\right)$ are complicated dimensionless scaling functions. Alternatively they can be written in the form $\mathcal{F}_{0,1}\left(\left(\frac{\kappa B}{\ell}\right)^2 \left(\frac{\kappa B}{\ell_{GC}}\right)^2, \kappa w, r\right)$. The salient features of dimensionless contributions to the surface tension and spontaneous curvature are presented in Fig. 5.1 and Fig. 5.2.

Fig. 5.1 shows that DLVO interaction renormalized surface tension tends in a monotonic way to the bare value, as the screening length is decreased, i.e. salt is added to the system, and is always positive, irrespective of the detailed values of the interaction parameters. The dependence on the charge ratio is more complicated and in general leads to non-monotonic behavior. The charge asymmetry thus engenders a minimum in the interaction renormalized surface tension, whose depth depends on
the amount of screening present in the system.

Fig. 5.2 shows analogous dependencies for the DLVO interaction renormalized curvature, but in this neither of the dependencies is monotonic. While the dependence on the charge asymmetry again shows a pronounced minimum at $r_{\text{min}} = \varepsilon_p/(\varepsilon_p - \varepsilon_w)$, whose depth depends on the salt screening, the dependence on the inverse Debye length can be either monotonic when $r \sim \pm 1$ or non-monotonic, when it is close to $r_{\text{min}}$. Furthermore, depending on the charge asymmetry parameter, the interaction renormalized spontaneous curvature can be either positive or negative. In the above numerical analysis we have not considered explicitly the variation of the dielectric spectrum of the capsid proteins as very little is presently known of its details.

5.4 Conclusion

Motivated by recent experiments, revealing that electrostatic interactions can be of paramount importance for the morphology of capsid-like aggregates and can fundamentally change the phase diagram of e.g. the CCMV capsid protein, where besides regions of single-wall and multi-wall capsids, tubes and free protein regions can be observed as a function of electrolyte solution parameters [112], we derived an interaction renormalization of the elastic properties of a proteinaceous shell of the virus capsid type. The interactions potentials taken into account are of the DLVO type, and by assumption composed of the vDW and electrostatic part. The first one considered on the level of the Lifshitz theory and the second one on the level of the linearized PB theory. This formulation of the problem then hinges only on mesoscale parameters characterizing the shell, such as the dielectric function of the capsid proteins, the magnitude of the dielectric discontinuity at the capsid-aqueous solvent boundary, capsid thickness, Debye screening length as well as the inner and the outer surface charge densities. Just as in the case of the DLVO theory of the stability of colloids,
microscopic details are not necessary to calculate the effect of the solution parameters on the magnitude of the spontaneous curvature.

The approach advocated here, avoiding all the microscopic details of the capsid shell composition, such as the internal structure of its proteins, possible non-isotropic dielectric response, detailed distribution of charged sites etc. obviously bypasses more detailed microscopic calculations, starting from the interaction free energy between capsomers and its dependence on their mutual orientation, that could be eventually translated into the spontaneous curvature of the shell. Just as more microscopic approaches to the colloid stability problem illuminate the mesoscale parameters used in the macroscopic DLVO approach, they could also fill in the details of our macroscopic description of the proteinaceous shells and our theory could be in principle refined, but with much effort and with the introduction of new, completely unknown and unquantified properties, like the anisotropic dielectric function of the proteinaceous shell, the inclusion of detailed charge dissociation equilibria for all the (de)protonated amino acids [128], or even explicit introduction of the non-DLVO interactions such as hydration and hydrophobic interactions [118]. We are convinced at this point that such a generalization, even if possible, would not clarify the problem but make it completely untransparent and unquantifiable. The thickness of the proteinaceous shell, confined to the narrow range of $\simeq 1.5-4.5$ nm [154], and comparable to the thickness of the lipid bilayers, does make our approach susceptible to criticism regarding the limitations of the continuum approach. While this criticism could be relevant, one should not gloss over different types of drawbacks of at first sight “exact” results, that could be provided by more detailed molecular simulations, based however on molecular potentials that as a rule compare poorly with the measured interaction potentials between (bio)macromolecules. Before model molecular potentials reach maturity, interim continuum results which can be expected to be qualitatively relevant, if not
quantitatively predictive, are the best we can do.

While the calculation of the surface tension and spontaneous curvature renormalization by the long-range DLVO potentials on the mesoscale level leaves no ambiguities in the results, the calculation of the renormalized bending rigidity is more sensitive to the detailed assumptions regarding the neutral surface with respect to which one renormalizes the long-range interaction part of the free energy. This is why we took the bending rigidity as a phenomenological parameter determined by the experiment.
Figure 5.1: Dependence of the dimensional scaling functions $\tilde{\sigma}$, Eq. (5.41), the surface charge ratio $r = \sigma_1/\sigma_2$ and different values of the inverse screening length, $\kappa$. The renormalized surface tension is always positive, tends to zero for large screening, but shows non-monotonic dependence on the charge asymmetry ratio.
Figure 5.2: Dependence of the dimensional scaling function $1/\tilde{R}_0$, Eq. (5.42), on the surface charge ratio $r = \sigma_1/\sigma_2$ and different values of the inverse screening length, $\kappa$. The renormalized curvature is in general a non-monotonic function of $r$ and $\kappa$, and can be of either sign depending on the charge asymmetry parameter and the amount of screening in the system.
APPENDIX
SUPPLEMENTARY DETAILS

Geometrical calculations of deformation of the vesicle while passing the pore

Partial sphere

First geometrical shape is a partial sphere with radius $r$ and the extracted angle $\theta$. For this shape we can easily get the volume to be

$$V = \frac{2}{3} \pi r^3 (1 + \cos \theta) \quad (A.1)$$

We can find area element $dA$ and integrate it over the surface to get total area, $A$.

$$dA = 2\pi r^2 \, d(\cos \theta) \quad (A.2)$$

$$A = \int dA = 2\pi r^2 \int_{-1}^{\theta} d(\cos \theta) = 2\pi r^2 (1 + \cos \theta)$$

One can easily find Gaussian ($K$) and Mean ($H$) curvature based on principal curvatures.

$$K = \frac{1}{r^2} \quad (A.3)$$

$$H = \frac{1}{r}$$
Cone

Next shape is a cone. We just need total volume of the cone in our work. if we define the radius of the bottom of the surface to be \(r\), and it has an angle \(\theta\), we will get

\[
V = \frac{1}{3} \pi r^2 h = \frac{1}{3} \pi r^3 \cot \theta \tag{A.4}
\]

cylinder

Cylinder is the part that is inside the pore, so the radius of cylinder (pore) is \(d\) and its length is \(l\). Total volume of the cylinder is

\[
V = \pi d^2 l \tag{A.5}
\]

we can write total area, and area element of the cylinder in the form of

\[
dA = 2\pi r dl \tag{A.6}
\]

\[
A = \int dA = 2\pi r \int_0^l dl = 2\pi rl
\]

and mean and Gaussian curvature are

\[
K = 0 \tag{A.7}
\]

\[
H = \frac{1}{2r}
\]

hemisphere

This part is similar to the partial sphere with \(\theta = \frac{\pi}{2}\) and replacing \(r\) with \(d\). This is the part that exist to avoid divergence in the free energy due to increased bending energy inside the pore. Its volume is

\[
V = \frac{2}{3} \pi r^3 \tag{A.8}
\]
Area element and total area respectively are

\[ dA = 2\pi r^2 d(\cos \theta) \]  \hspace{1cm} (A.9)  
\[ A = \int dA = 2\pi r^2 \int_{-1}^{0} d(\cos \theta) = 2\pi r^2 \]

and curvature is equal to a normal surface

\[ K = \frac{1}{r^2} \]  \hspace{1cm} (A.10)  
\[ H = \frac{1}{r} \]

**Partial Torus**

This is the connecting part between the partial sphere and pore. Its outer radius is \( c = (b + d) \) with inner radius of \( d \). \( \nu \) is the angle around the big circle and it is limited to \( \frac{\pi}{2} + \theta \) and \( \pi \). Its volume is

\[ V = \pi b^2 c \left( \frac{\pi}{2} - \theta \right) - \frac{2\pi}{3} b^3 \cos \theta. \]  \hspace{1cm} (A.11)

Writing surface area element and integrate over the surface with give us \( A \).

\[ dA = 2\pi b \left[ c + b \cos \nu \right] d\nu \]  \hspace{1cm} (A.12)
\[ A = \int dA = 2\pi b \int_{\frac{\pi}{2}+\theta}^{\pi} \left[ c + b \cos \nu \right] d\nu = 2\pi b \left[ c \left( \frac{\pi}{2} - \theta \right) - b \cos \theta \right] \]

With some calculations we can find principle curvatures, and since Mean and Gaussian curvatures are respectively equal to average of those two and products of them, we will get
\[ K = \frac{\cos \nu}{b [c + b \cos \nu]} \quad \text{(A.13)} \]

\[ H = -\frac{c + 2b \cos \nu}{2b [c + b \cos \nu]} \quad \text{(A.14)} \]

**Introduction to Lerch functions**

The definition of the *Lerch transcendental* function in the standard form is

\[ \Phi(z, s, \nu) = \sum_{n=0}^{\infty} \frac{z^n}{(\nu + n)^s}. \quad \text{(A.15)} \]

Obviously the polylog function can be expressed as

\[ Li_s(z) = \sum_{k=0}^{\infty} \frac{z^k}{k^s} = z\Phi(z, s, 1), \quad \text{(A.16)} \]

and the more familiar Riemann zeta function then follows as

\[ \zeta(s) = Li_s(1) = \Phi(1, s, 1) \quad \text{(A.17)} \]

The analytical continuation of the *Lerch* function is particularly appropriate to evaluate the integrals of the Lifshitz part of the spheroidal shell free energy expansion and can be written in the canonical forms

\[ \int_0^\infty dx \frac{x^{\nu-1}e^{-\mu x}}{1 - \beta e^{-x}} = \Gamma(\nu) \Phi(\beta, \nu, \mu) \]

\[ \int_0^\infty dx \frac{x^{\nu-1}e^{-\mu x}}{(1 - \beta e^{-x})^2} = \Gamma(\nu) [\Phi(\beta, \nu - 1, \mu) - (\mu - 1)\Phi(\beta, \nu, \mu)] \quad \text{(A.18)} \]

where \( \Gamma(x) \) is the gamma function. The exact expressions we used in Chapter 5 for Lifshitz free energy curvature expansion are of the form

\[ \int_0^\infty dx \ x \log \left( 1 + \Delta^* e^{-2x} \right) = -\frac{1}{4} Li_3(\Delta^*) \quad \text{(A.19)} \]
as well as
\[
\int_0^\infty dx \frac{x^{\nu-1} e^{-2x}}{1 + \Delta^* e^{-2x}} = \frac{1}{2^{\nu}} \Gamma(\nu) \Phi(-\Delta^*, \nu, 1) \tag{A.20}
\]
and
\[
\int_0^\infty dx \frac{x^{\nu-1} e^{-4x}}{(1 + \Delta^* e^{-2x})^2} = \\
= \frac{1}{2^{\nu}} \Gamma(\nu) [\Phi(-\Delta^*, \nu - 1, 2) - \Phi(-\Delta^*, \nu, 2)]. \tag{A.21}
\]

We obtain values of all the integrals in the curvature expansion of the Lifshitz interaction energy using Lerch functions. For further information regarding these functions, please see [57]
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