INTERACTIONS AND CONFORMATIONAL FLUCTUATIONS IN MACROMOLECULAR ARRAYS

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1. Introduction and outline

I will review the work on the equation of state in macromolecular arrays, meaning mostly ordered hexagonal DNA arrays and ordered multilamellar lipid membrane arrays. First I will discuss the interactions between charged macromolecules of different geometrical shape, such as DNA cylinders and planar lipid bilayers, and then develop a statistical mechanical theory for the equation of state that will include also conformational fluctuations of the macromolecules in the array. I will start with a very simple model and then refine it to the extent that the theoretically derived results become comparable with experiments. Further on I will analyze the way bare interactions couple with fluctuations and draw some general conclusions regarding their importance in ordered DNA arrays and ordered multilamellar lipid membrane arrays. The main difference in behaviors of the two systems stems as much from a different internal geometry (1D for polymers vs. 2D for membranes) as well as from the fact that in condensed DNA phases the positional order is short ranged (liquid like) while it is quasi long ranged (smectic) in membrane assemblies. I will conclude by examining the interaction renormalization of the bending moduli of DNA in hexagonal arrays and of lipid membranes in multilamellar arrays. From here I will show that in the low salt limit the effect of conformational fluctuations on the equation of state becomes negligible. In this case the osmotic pressure stemming only from the counterions can account for most of the available experimental data. The lecture will thus give a comprehensive introduction to the equation of state for both types of biological macromolecules under various solution conditions with monovalent salts and counterions.

In the phase diagram of DNA in aqueous solutions there is a range extending from the DNA crystal at densities corresponding to interaxial separations below ≈ 24 Å all the way to the nematic - isotropic transition at densities corresponding to interaxial separations ≈ 120 Å (for a bathing solution of 0.5 M NaCl) where DNA is orientationally ordered or even shows long range hexatic order perpendicular to the long axes of the molecules but is positionally still a liquid with only short range positional order [1]. Similarly there is a range of lipid concentrations well above the CMC where lipids exist in bilayer form making a lamellar L_α phase with quasi long range positional order of the lamellae [2] where fluctuations in the local positions depend only weakly (logarithmically) on the size of the sample.

In this part of the phase diagram of both systems, the equation of state, *i.e.* the dependence of the osmotic pressure on the macromolecular (DNA or lipid) concentration, has been studied very carefully. In this lecture I will make an attempt to explain in all necessary detail the theoretical underpinnings of these equations of state. It would suit my purposes ideally if I could compare the equation of state of a charged linear polymer such as DNA with the equation of state of charged lipid bilayers, but the experiments performed up to this time do not permit that quite yet. There are persistent salt equilibration problems in the multilamellar lipid case that have not yet been fully overcome. Nevertheless I believe that even the comparison of the behavior of DNA arrays with neutral lipid membrane arrays is definitively worth a try.

2. DLVO interactions

DLVO forces [3], refer to the (Poisson - Boltzmann or Debye-Hückel) mean-field screened electrostatic interactions and Lifshitz - van der Waals electromagnetic fluctuation forces in the context of pairwise interaction between charged cylindrical and planar macromolecules.

2.1. POISSON-BOLTZMANN THEORY

We start by writing down the expression for the non-equilibrium mean-field free energy density (f) of a gas of mobile charged particles *i.e.* counterions and salt ions. It can be written as a difference of the electrostatic field energy

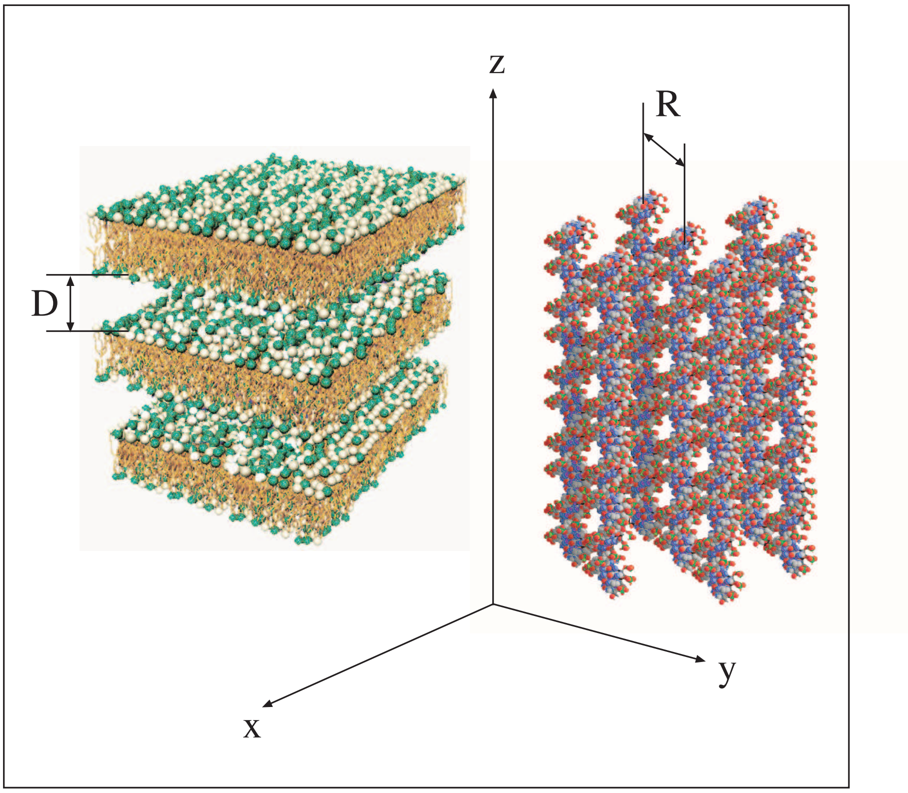

Figure 1. The schematic geometry of an array of DNA molecules with long range orientational order and short range positional order and an array of lipid membranes in the L_α with quasi-long range positional order. Both are drawn approximately to scale. Adapted in part from Rädler JO, Koltover I, Salditt T, Safinya CR *Science* **275** 78-81 (1997).

density (w) and the ideal entropy density of the mobile charge carriers (s)

$$\begin{aligned} f(\mathbf{E}(\mathbf{r}), \rho_i(\mathbf{r})) &= w - Ts \\ &= \tfrac{1}{2}\epsilon\epsilon_0 \mathbf{E}^2(\mathbf{r}) + kT \sum_i \left(\rho_i(\mathbf{r}) ln\left(\frac{\rho_i(\mathbf{r})}{\rho_i^0}\right) - (\rho_i(\mathbf{r}) - \rho_i^0)\right), \end{aligned} \tag{1}$$

where $\mathbf{E}(\mathbf{r}) = -\boldsymbol{\nabla}\phi(\mathbf{r})$ is the local electric field that satisfies the Poisson equation

$$\epsilon\epsilon_0 \,\mathrm{div}\mathbf{E}(\mathbf{r}) = \sum_i e_i \rho_i(\mathbf{r}). \tag{2}$$

Here ϵ is the static dielectric constant, kT is the thermal energy, $\rho_i(\mathbf{r})$ is the density of the mobile charge carrier i and ρ_i^0 is the charge density of the mobile charged species i in the reservoir. By minimizing the free energy given by the volume integral of Eq. 1 with respect to the electric field and taking into account the Poisson equation Eq. 2, one obtains the Poisson - Boltzmann equation in the form

$$\boldsymbol{\nabla}^2\phi(\mathbf{r}) = -\frac{1}{\epsilon\epsilon_0}\sum_i \rho_i(\phi(\mathbf{r})) = -\frac{e_0 n_0}{\epsilon\epsilon_0}\sum_i z_i e^{-\beta z_i e_0 \phi(\mathbf{r})}, \tag{3}$$

that gives the equilibrium profile of the electric field in the system. If the magnitude of the surface charges is not too large, one has $\beta e_0\phi(\mathbf{r}) \ll 1$. The Poisson - Boltzmann equation can be linearized and reduced to the Debye - Hückel equation [4] that describes screened electrostatic interactions with a screening (Debye) length equal to $\lambda_D = \left(\sum_i \frac{e_0^2 n_0 z_i^2}{\epsilon\epsilon_0 kT}\right)^{-1/2}$.

The forces between macromolecules mediated by the equilibrium distribution of counterions and salt ions between them can be obtained by either of two approaches. In the first approach one evaluates the stress tensor, composed of the Maxwell and the osmotic part,

$$\sigma_{ij} = \epsilon\epsilon_0\left(E_iE_j - \tfrac{1}{2}E^2\delta_{ij}\right) + kT\sum_i \rho_i(\phi(\mathbf{r}))\delta_{ij}, \tag{4}$$

at an appropriate plane of symmetry of the interacting molecules. In many cases it is simplest to take the stress tensor at the surface of the macromolecules, in which case the forces are obtained *via* a contact theorem [5], or at the symmetry plane in the middle of the space between the two macromolecules. If the line joining them is along the z axis and S is the plane perpendicular to it, the force between two charged macromolecules is obtained as

$$F = \int_S d^2\mathbf{r}\ (\sigma_{zz}(z=0) - \sigma_{zz}^{(0)}) = \int_S d^2\mathbf{r}\ (\sigma_{zz}(z=D/2) - \sigma_{zz}^{(0)}), \tag{5}$$

where $z = 0$ stands symbolically for the midplane position, $z = D/2$ for the surface of the macromolecule and $\sigma_{zz}^{(0)}$ is the stress tensor in the bulk.

Another approach would be to evaluate the complete equilibrium free energy $\mathcal{F}$ from Eq. 1 *via* a volume integral over all the space available to the mobile charges

$$\mathcal{F} = \int d^3\mathbf{r}\ f(\mathbf{E}(\mathbf{r}), \rho_i(\mathbf{r})) \tag{6}$$

where the electrostatic field and the densities of the mobile charges are obtained from the solution of the full or linearized Poisson - Boltzmann equation Eq. 3. The forces between charged bodies are then obtained as a derivative of the free energy with respect to the separation D between the bodies

$$F = \left(\frac{\partial \mathcal{F}}{\partial D}\right)_{T,\mu}, \tag{7}$$

at constant temperature and chemical potential of the mobile charged species.

2.2. INTERACTION BETWEEN CYLINDRICAL MACROMOLECULES

The mean-field electrostatic interaction can be explicitly evaluated on the Debye - Hückel level [6, 7], assuming that in an aggregate of long cylindrical molecules with local hexagonal symmetry the interactions are pairwise additive, resulting in an interaction potential or mean-field interaction free energy $\mathcal{F}(R)$ between two parallel charged rods of radius a, length L and at an interaxial separation R of the form [8]

$$\mathcal{F}(R) = kT\frac{\ell_B}{b^2}K_0(R/\lambda_D)\ L \tag{8}$$

where $\ell_B = e_0^2/4\pi\epsilon\epsilon_0 kT$ is the Bjerrum length, being 7.4 Å for water at room temperature. For monovalent salts with ionic strength $I = \sum_i n_0 z_i^2$ expressed in moles [M] per liter, $\lambda_D = 3.08$ Å $/\sqrt{I[M]}$. Eq. 8 refers to two cylinders with surface charge density σ, modeled as two infinitely thin lines with a linear charge density described *via* an effective separation b between charges along the line $1/b = 2\pi\sigma\lambda_D/e_0 K_1(a/\lambda_D)$ [9] (for DNA $b = l_{PO_4}$, where $l_{PO_4} \sim 1.7$ Å is the separation between the phosphate charges along DNA [10]). For large d/λ_D the Bessel function K_0 can be approximated by $K_0(d/\lambda_D) \approx \sqrt{\frac{\pi}{2}}\frac{e^{-R/\lambda_D}}{\sqrt{R/\lambda_D}}$.

In the case of very large surface charges the nonlinearities of the Poisson-Boltzmann equation effectively change the surface charge density entering the above equation Eq. 8 *via* $b \longrightarrow \ell_B$ while leaving the separation dependence largely unaltered. Sometimes these non-linearity effects, that become pronounced depending on whether the s.c. Manning parameter $\zeta = l_B/b$ is larger or smaller than one, would be referred to as Manning condensation [8]. Thus for two parallel molecules in the limit of large linear charge densities the interaction free energy would assume the form

$$\mathcal{F}(R) = \frac{kT}{\ell_B}K_0(R/\lambda_D)\ L. \tag{9}$$

Besides the mean-field forces due to the fixed charge distribution on the macromolecules one also has the forces due to the fluctuating electromagnetic fields permeating the space in and around the cylinders. These macroscopic van der Waals interactions can be computed in the framework of the Lifshitz theory [11] and are thus referred to as Lifshitz - van der Waals interactions. In this framework the fluctuation interactions are determined by the frequency (ω) dependence of the dielectric functions of the interacting macromolecules parallel ($\epsilon_{||}(\omega)$) and perpendicular ($\epsilon_{\perp}(\omega)$) to the long axis as well as the dielectric function ($\epsilon_m(\omega)$) of the bathing medium, *i.e.* an aqueous solution, and lead [12] to the interaction free energy between two parallel cylindrical macromolecules of the form

$$\mathcal{F}(R) = -\frac{3\ kT}{8\pi}\left(\pi a^2\right)^2 \mathcal{A}\frac{L}{R^5}, \tag{10}$$

where I introduced the Hamaker constant $\mathcal{A}$ as

$$\mathcal{A} = \sum_{n=0}^{\infty}{}' \left(\Delta_{\perp}^2(i\omega_n) + \tfrac{1}{4}\Delta_{\perp}(i\omega_n)\Gamma(i\omega_n) + \tfrac{3}{2^7}\Gamma^2(i\omega_n)\right), \tag{11}$$

as is usually done in the framework of the DLVO theory [13]. The primed summation means that the $n = 0$ term should be taken with a weight $\frac{1}{2}$. Also I have assumed that the magnetic properties of all the media involved are the same. I have used the following abbreviations $\Delta_{||}(i\omega_n) = (\epsilon_{||}(i\omega_n) - \epsilon_m(i\omega_n))/(\epsilon_m(i\omega_n))$, $\Delta_{\perp}(i\omega_n) = (\epsilon_{\perp}(i\omega_n) - \epsilon_m(i\omega_n))/(\epsilon_{\perp}(i\omega_n) + \epsilon_m(i\omega_n))$ and $\Gamma(i\omega_n) = \Delta_{||}(i\omega_n) - 2\Delta_{\perp}(i\omega_n)$. The dielectric response at imaginary frequencies $\epsilon(i\omega)$ can be shown *via* the Kramers - Kronig relations to be a monotonic function of ω. In the case that the bathing medium is an electrolyte solution the $n = 0$ term in the Hamaker constant is exponentially screened with half the Debye length [11].

Apart from the van der Waals forces one also has attractive counterion correlation forces, which account for all the thermal effects not taken into account on the Poisson-Boltzmann (mean-field) level and will be introduced in other lectures [4, 11]. They are usually negligible for univalent salts and/or counterions, the case addressed in these lecture notes.

It turns out that after we insert the appropriate numbers for $\epsilon_{||}(\omega)$ and $\epsilon_{\perp}(\omega)$ valid for DNA [10], the Lifshitz - van der Waals interaction in the whole regime of DNA densities investigated in this lecture is about two orders of magnitude smaller than the mean-field repulsive interactions and can thus be safely ignored.

2.3. INTERACTIONS IN PLANAR ARRAYS OF MACROMOLECULES

In the case of interacting planar macroions of surface area S in a multilamellar aggregate the interaction free energy is again straightforward to calculate. Andelman [14] has defined several regions in the parameter space where explicit forms for the interaction free energy can be written down. In the Debye-Hückel region [15] corresponding to $\lambda_{DH} \ll D$, where D is the surface to surface separation between the neighboring lamellae, with small surface charge

$$\mathcal{F}(D) = \frac{kT\lambda_D}{\pi \ell_B b^2}\left(\mathrm{cth}(\kappa D) - 1\right) S, \tag{12}$$

where the separation of charges on the surface is given by the Gouy-Chapman length $b = e_0/8\pi^2|\sigma|\ell_B$. In the same range of D but with large surface charge density , one can use the superposition approximation, at the midplane obtaining

$$\mathcal{F}(D) = \frac{8\ kT}{\pi \lambda_D l_B}\ e^{-\kappa D} S. \tag{13}$$

Just as in the case of cylindrical macromolecules one also has the forces due to fluctuating electromagnetic fields permeating space in and around the macromolecules. If the dielectric function of the macromolecule, *i.e.* the lipid bilayer, is $\epsilon_l(\omega)$ and that of the intervening aqueous solution $\epsilon_m(\omega)$ then the unretarded van der Waals interaction between two semi-infinite regions of dielectric material m over a slab of thickness D is [13]

$$\mathcal{F}(D) = -\frac{\mathcal{A}}{12\pi D^2}\ S, \tag{14}$$

where S is the surface area and the Hamaker constant in planar geometry has been defined as

$$\mathcal{A} = \tfrac{3kT}{2} {\sum_{n=0}^{\infty}}' \int_0^{\infty} u\ du\ \ln\Big(1 - \big(\tfrac{\epsilon_m(i\omega_n) - \epsilon_l(i\omega_n)}{\epsilon_m(i\omega_n) + \epsilon_l(i\omega_n)}\big)^2 e^{-2u}\Big). \tag{15}$$

Again I have assumed that the magnetic properties of all the media involved are the same. If the two macromolecular regions are of finite width then the dependence of the interaction energy on D is modified [11].

Here we have omitted the effects of retardation assuming that the separation between the macromolecules is small enough. As in the case of cylindrical macromolecules I will not address the counterion correlation forces since they form the subject matter of other lectures [4].

Contrary to the case of DNA, the Lifshitz - van der Waals interactions in lipid membrane arrays immersed in an aqueous solution are comparable in magnitude to the mean-field electrostatic repulsions and can in general not be ignored. For most lipid membranes interacting across an aqueous solution a typical value of the Hamaker constant is estimated to lie in the range $10^{-13} - 10^{-14}$ ergs [3, 16]. If the aqueous solution is in fact an electrolyte solution the $n = 0$ term of the Hamaker constant is again exponentially screened with half the Debye length of the electrolyte solution.

3. Non-DLVO forces

One of the (many) important assumptions in the foundations of the Poisson - Boltzmann and Lifshitz - van der Waals interactions is that water is a structureless medium that can be characterized solely through its frequency dependent dielectric response and that the interacting macromolecules can be characterized solely through their continuous charge distribution on their surface. Theoretical work as well as numerous experiments suggest that at small separations between interacting molecules progressively more and more of the molecular details of the bathing solvent as well as interacting surfaces come into play when one tries to understand the nature of the interactions in the last few Angstroms. We still have no clear and widely accepted theoretical picture of the state of affairs in this regime of intersurface separations.

There is however no need to stay in this limbo since the experiments suggest [16] that these short range (SR) interactions whatever they might be due to, can in many cases be described *via* a semi-empirical force law of the form

$$\begin{aligned} \mathcal{F}_{SR}(D) &= F_0\ e^{-D/\xi} S \\ \mathcal{F}_{SR}(R) &= F_0\ K_0(R/\xi) L. \end{aligned} \tag{16}$$

where the first equation is valid for the short range interactions between planar macromolecules and the second one between cylindrical macromolecules. The numerical value of ξ is between $1-3$ Å[16, 17]. I will use this empirical form $\mathcal{F}_{SR}$ of the interaction free energy together with the mean-field electrostatic $\mathcal{F}_{ES}$ and Lifshitz - van der Waals interactions $\mathcal{F}_{vdW}$ in order to have an interaction free energy expression valid in the whole regime of intersurface separations.

Without going too much off the track let me just state that it seems quite probable that most of the effects described by Eqs. 16 are due to the structure and structuring effects of water close to molecular surfaces. Therefore one often refers to this short range interaction as hydration interaction.

4. Equation of state for hexagonal and multilamellar assemblies

An equation of state in general means a connection between the osmotic pressure Π and the macromolecular density ρ of the assembly

$$\Pi = \Pi(\rho) \tag{17}$$

and is thus obtained *via* a complete statistical mechanical treatment of a solution composed of cylindrical or planar macromolecules and the bathing medium. While the intermolecular degrees of freedom are taken into account through interaction potentials described in the previous two sections, the intramolecular degrees of freedom are usually treated within a mesoscopic elastic model that substitutes macroscopic elasticity for the complicated short-range intramolecular potentials acting between different segments of the macromolecules [18]. Though it would seem off hand a bit far fetched to expect that macroscopic elasticity can satisfactorily describe the complex short ranged intramolecular interactions it turns out that this indeed is so.

Elastic models for cylindrical and planar macromolecules have been well worked out [19]. The general idea is that the trace over all the microscopic degrees of freedom is assumed to result exactly in the mesoscopic Hamiltonian itself that one now uses in the partition function to evaluate the trace over mesoscopic degrees of freedom.

A most naive approach to the equation of state would be to simply forget the intramolecular degrees of freedom, assume that the macromolecules are ideally rigid and assemble into a crystal of either lamellar or hexagonal symmetry with perfect positional order. In this case the osmotic pressure of such a system can be obtained *via* Ewald force summation (in the case of short range interactions even this is dispensable) involving the intermolecular potentials leading directly to the equation of state. For the multilamellar array the equation of state would thus read

$$\Pi(\rho) = -\left(\frac{\partial(\mathcal{F}(D)/S)}{\partial D}\right)_{T,\mu} \qquad \mathcal{F} = \mathcal{F}_{SR} + \mathcal{F}_{vdW}, \quad \rho = \frac{1}{D}, \tag{18}$$

where S is the area of the lamellae, D is the interlamellar separation and ρ is the one-dimensional density. The free energy contains only the short range (hydration) part and the van der Waals part. As I already noted in the introduction I shall limit myself mostly to the case of uncharged lipid bilayers where there are no pertinent salt equilibration problems. Note that all the contributions to the free energy scale linearly with area S.

For the hexagonal array of DNA molecules the corresponding equation of state can be obtained from

$$\Pi(\rho) = -\left(\frac{\partial(\mathcal{F}(D)/L)}{\sqrt{3}\; R\partial R}\right)_{T} \qquad \mathcal{F} = \mathcal{F}_{SR} + \mathcal{F}_{ES}, \quad \rho = \frac{2}{\sqrt{3}\; R^2}. \tag{19}$$

L is the length of the molecules in the array and ρ is now the two-dimensional density. Note that there is no van der Waals contribution (see above) to the free energy in this case and that all the parts of the total free energy scale linearly with length L of the molecules.

We can now take these equations of state and compare them to experiments performed on DNA [20] and lipid membrane arrays [21] composed of neutral lipids DPPC and DMPC. Performing this type of exercise one is immediately convinced that something crucial is missing as there is practically no correspondence (except at very high densities) between the experiment and this type of simpleminded theory, see Fig. 2. For the multilamellar case I have taken $H = 4 \times 10^{-14}$ ergs [3, 16] and the magnitude of the short range interactions is obtained from the fit to the data at high macromolecular densities as $F_0 = 2.1 \times 10^1 erg/cm^2$ for lipids and $F_0 = 1.3 \times 10^{-7} erg/cm$ for DNA. In the case of DNA the magnitude of the surface charge is taken at the Manning value [8]. Obviously this equation of state underestimates the energetics of the system.

5. The effect of thermal fluctuations

I now relax the constraint that the macromolecules in the array are ideally stiff and describe them as deformable elastic bodies *via* mesoscopic elasticity theory [18, 19]. Since I am dealing with an array I might as well construct a mesoscopic elastic Hamiltonian for the whole array. Because in the regime of relevant densities the hexagonal array is either in the line hexatic or the cholesteric phases [20] and the multilamellar array is in the smectic L_α phase [2] I can use the mesoscopic elastic Hamiltonians pertaining to them. The goal here will be to combine the effects of thermally driven elastic fluctuations of the macromolecules with the interactions between them and calculate their combined effect on the equation of state.

This approach is based on ideas first introduced by Helfrich in the '70's and later worked out in detail by Lipowsky, Leibler and others in the '80's [22], who showed in the context of membranes that thermal motion can have a profound effect on interactions between flexible macromolecules. In this lecture we will limit ourselves to the regime of macromolecular densities higher than the cholesteric-isotropic transition of DNA or the unbinding transition for lipid membranes, deeply within the ordered phase. Thus: no phase transitions.

5.1. A MACROSCOPIC THEORY OF THE EQUATION OF STATE IN A HEXAGONAL ARRAY

Let us first consider the elastic free energy of a nematic: a three dimensional liquid with long-range orientational order with an average director $\mathbf{n}$ along the z-axis. We forget about the hexatic or even the cholesteric order because it is on a much larger scale then the nematic order. There are three kinds of deformations to quadratic order in $\mathbf{n}$ with symmetry $C_{\infty h}$ [18]: splay, twist and bending. The corresponding elastic constants for these deformations are the Frank constants K_1, K_2 and K_3 [23]. For small deviations of the director field $\mathbf{n}(\mathbf{r})$ around its average orientation along the z axis $\mathbf{n}(\mathbf{r}) \approx$

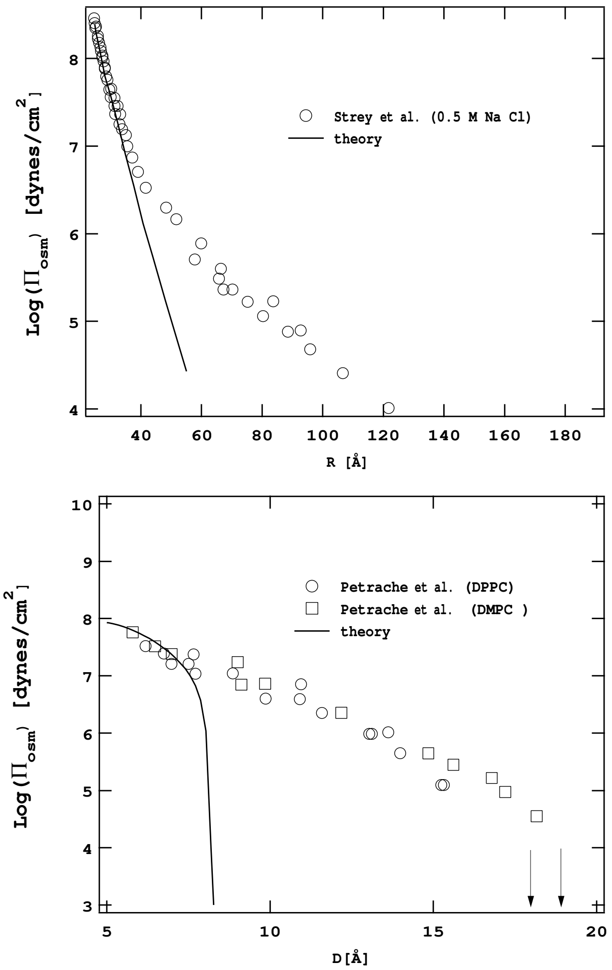

Figure 2. A fit of the equations of state Eqs. 18 and 19 to the DNA [20] and lipid membranes, composed of neutral lipids DPPC and DMPC, [21] experiments. Obviously there are large discrepancies on this level between the theoretical predictions and actual data. The arrows indicate the stable equilibrium separation at zero osmotic pressure.

$(\delta n_x(\mathbf{r}), \delta n_y(\mathbf{r}), 1)$, with $\mathbf{r} = (z, \mathbf{r}_\perp)$ the free energy assumes the form

$$\mathcal{F}_N = \tfrac{1}{2} \int d^2\mathbf{r}_\perp dz \left[K_1 \left(\nabla_\perp . \delta\mathbf{n}\right)^2 + K_2 \left(\nabla_\perp \times \delta\mathbf{n}\right)^2 + K_3 \left(\partial_z \delta\mathbf{n}\right)^2 \right] \quad (20)$$

For polymer nematics we have to consider the fact that the director field and the density of polymers $\rho = \rho_0 + \delta\rho$ are coupled [24]. If the polymers were infinitely long and stiff the coupling would be given by the continuity equation for the director field:

$$\partial_z \delta\rho + \rho_0 \nabla_\perp . \delta\mathbf{n} = 0. \tag{21}$$

This constraint, however, is softened if the polymer has a finite length ℓ or a finite elastic modulus K_c. On length scales larger than ℓ or K_c/kT the polymer can either fill the voids with its own ends or fold back on itself and can splay without any density change [20]. Following [25, 26] this can be expressed by introducing a Lagrange multiplier G, a measure of how effectively the constraint Eq. 21 is enforced. Density changes are then expanded to second order in density deviations $\delta\rho(\mathbf{r}_\perp, z) = \rho(\mathbf{r}_\perp, z) - \rho_0$. $\mathcal{B}$ is the polymer solution bulk compressibility modulus. The total mesoscopic free energy, or equivalently the mesoscopic Hamiltonian $\mathcal{H}$ is now obtained in the form [27]

$$\mathcal{H} = \mathcal{F}_0(\rho_0) + \tfrac{1}{2} \int d^2\mathbf{r}_\perp dz \left[\mathcal{B} \left(\tfrac{\delta\rho}{\rho_0} \right)^2 + G \left(\partial_z \delta\rho + \rho_0 \nabla_\perp . \delta\mathbf{n} \right)^2 \right] + \mathcal{F}_N \tag{22}$$

where G is given by

$$G = \frac{k_B T \ell}{2\rho_0}, \tag{23}$$

with ℓ never to exceed K_c/kT [26]. In the limit of finite polymer length G is also finite and can be obtained from the observation that $\partial_z \delta\rho + \rho_0 \nabla_\perp . \delta\mathbf{n}$ equals the difference between the number of chain heads and tails [26].

In order to calculate the contribution to the free energy due to thermal fluctuations on the mesoscopic scale one has to take a trace of $\exp(-\beta\mathcal{H})$ with respect to density and nematic director fluctuations. The macroscopic free energy that now contains also the contributions of the thermal fluctuations on the mesoscopic scales described by the Hamiltonian Eq. 22 can be obtained as

$$\mathcal{F} = -kT \ln \langle e^{-\beta\mathcal{H}} \rangle = \tfrac{1}{2}\, k_B T \iint \tfrac{d^2 q_\perp dq_z}{(2\pi)^3} \ln \left(K_1 q_\perp^2 q_z^2 + K_3 q_z^4 + \mathcal{B} q_\perp^2 \right). \tag{24}$$

The problem now is that the above integral requires a cutoff meaning that the higher order terms in $q_\perp$ are more important than the ones we have kept here. For a moment let us assume that this free energy is nevertheless valid and we may calculate

$$\begin{aligned} \frac{\partial \mathcal{F}}{\partial \mathcal{B}} &= \tfrac{1}{2}\, k_B T V \iint \tfrac{q_\perp dq_\perp dq_z \;\; q_\perp^2}{(2\pi)^2 \;\; K_1 q_\perp^2 q_z^2 + K_3 q_z^4 + \mathcal{B} q_\perp^2} \\ &= \tfrac{k_B T \; V}{16\pi} \int \frac{q_\perp^3 \, dq_\perp}{\sqrt{\mathcal{B} q_\perp^2} \sqrt{K_1 q_\perp^2 + 2\sqrt{\mathcal{B} K_3 q_\perp^2}}}. \end{aligned} \tag{25}$$

This integral depends essentially on the upper cutoff for $q_\perp = q_{\perp max}$ and we obtain

$$\frac{\partial \mathcal{F}}{\partial \mathcal{B}} = k_B T \frac{V}{4\pi} \frac{\mathcal{B} K_3}{K_1^2 \sqrt{\mathcal{B} K_1}} \; F\left(\frac{q_{\perp max}}{2\sqrt{\frac{\mathcal{B} K_3}{K_1^2}}} \right), \tag{26}$$

where the function $F(x)$ has been defined as $F(x) = \int_0^x \frac{u^{3/2} du}{\sqrt{1+u}}$. From here we obtain the two limiting forms of the free energy as

$$\mathcal{F} \simeq \frac{k_B T \; V}{5 \times 2^{3/2} \pi} \sqrt[4]{\frac{\mathcal{B}}{K_3}} \; q_{\perp max}^{5/2} + \dots \qquad ; \; q_{\perp max} \ll 2 \sqrt{\frac{\mathcal{B} K_3}{K_1^2}} \tag{27}$$

$$\mathcal{F} \simeq \frac{k_B T \; V}{16\pi} \sqrt{\frac{\mathcal{B}}{K_1}} \; q_{\perp max}^{2} + \dots \qquad ; \; q_{\perp max} \gg 2 \sqrt{\frac{\mathcal{B} K_3}{K_1^2}}. \tag{28}$$

Obviously the long-wavelength physics is very complicated and depends crucially on the values of typical polymer length and the ratios of elastic constants. However it is also dependent on the $q_\perp$ cutoff. We have to either eliminate the cutoff by including higher order terms in the original Hamiltonian or choose a meaningful cutoff.

One can show [20] that a consistent value of the cutoff has to be proportional to the "Brillouin zone" radius $q_{\perp max} \simeq \frac{\pi}{R}$, where R is the effective separation between the polymers in the nematic phase. This is a physically meaningful and appropriate cutoff because the underlying macroscopic elastic model has, by definition, to break down at wavelengths comparable to the distance between molecules.

Putting in the numbers valid for DNA arrays one realizes that in the regime of densities considered here we are always in the Eq. 27 limit.

We would now have to derive the mesoscopic elastic moduli from the microscopic interactions described *via* a pair potential $U(\mathbf{r})$ (the interaction free energy) between the segments of the macromolecules. At present this program is too ambitious and we simply exploit the standard *ansatz* for the different elastic moduli [23]

$$\begin{aligned} K_1 &= K_2 \simeq U(R)/R \\ K_3 &\simeq \rho_0 K_c + U(R)/R \\ \mathcal{B} &\simeq V \frac{\partial^2 \mathcal{F}_0(V)}{\partial V^2} = \frac{\sqrt{3}}{4} \left(\frac{\partial^2 (\mathcal{F}/L)}{\partial^2 R} - \frac{1}{R} \frac{\partial (\mathcal{F}/L)}{\partial R}. \right), \end{aligned} \tag{29}$$

where ρ_0 is the 2D density of the macromolecules perpendicular to their long axes, K_c is the elastic rigidity modulus of a single polymer molecule and we assumed that the polymers have a local hexagonal packing symmetry with an average separation R between first neighbors [20].

Using now the form of the bare interaction free energy $\mathcal{F}(R) = \mathcal{F}_{SR}(R) + \mathcal{F}_{ES}(R)$ appropriate for a DNA array (see above) including the short range and the electrostatic part of the interaction as well as the fact that at all relevant densities $K_3 \sim eq\rho_0 K_c$, we are able to fit the calculated equation of state obtained from Eq. 27 to the experimental equation of state [20], see Fig. 3. The values for the DNA bending rigidity and the Debye length obtained from such a fit are comfortably within the expected range [20]. It is a bit surprising that the effective charge is about half the amount expected on the basis of the Manning condensation theory.

5.2. A MACROSCOPIC THEORY OF THE EQUATION OF STATE IN A LAMELLAR ARRAY

For lipid membranes the evaluation of the equation of state from the mesoscopic Hamiltonian is simpler because the director field and the density of the membranes along the (z)-axis are not coupled [23]. The free energy is thus composed of the elastic free energy of the membranes and the compressional free energy perpendicular to the planes of the membranes [18].

For small deviations of the director field $\mathbf{n}(\mathbf{r})$ (that is taken in the direction of the local normal to the bilayer surfaces) from its average direction taken along the z axis, $\mathbf{n}(\mathbf{r}) \approx (\delta n_x(\mathbf{r}), \delta n_y(\mathbf{r}), 1)$, the nematic free energy takes the form [23]

$$\mathcal{H}_N = \tfrac{1}{2} \int d^2\mathbf{r}_\perp dz \left[K_1 \left(\nabla_\perp . \delta\mathbf{n}\right)^2 + K_2 \left(\nabla_\perp \times \delta\mathbf{n}\right)^2 + K_3 \left(\partial_z \delta\mathbf{n}\right)^2 \right]. \quad (30)$$

Furthermore since one assumes that the deviations of the membranes from the planar shape are small, we have to the lowest order $\delta\mathbf{n}(\mathbf{r}) \simeq (1, \nabla_\perp u(\mathbf{r}_\perp, z))$, where $u(\mathbf{r}_\perp)$ is the local deviation of the membranes from the plane in the z direction. Since the density and the nematic deformation in smectic arrays are not coupled, one has $\delta\rho/\rho \simeq \frac{\partial u(\mathbf{r}_\perp, z)}{\partial z}$. One obtains for the mesoscopic Hamiltonian to the quadratic order [23]

$$\begin{aligned} \mathcal{H} &= \tfrac{1}{2}\mathcal{B} \int d^2\mathbf{r}_\perp dz \left(\tfrac{\delta\rho}{\rho_0}\right)^2 + \mathcal{H}_N = \\ &= \tfrac{1}{2}\mathcal{B} \int d^2\mathbf{r}_\perp dz \left(\tfrac{\partial u(\mathbf{r}_\perp, z)}{\partial z}\right)^2 + \tfrac{1}{2}K_1 \int d^2\mathbf{r}_\perp dz \left(\nabla_\perp^2 u(\mathbf{r}_\perp, z)\right)^2. \quad (31) \end{aligned}$$

Summing now over all the displacement modes in Fourier space just as in the case of the hexagonal array, yields the following form of the macroscopic free energy

$$\mathcal{F} = -kT \; ln\langle e^{-\beta\mathcal{H}}\rangle = \tfrac{1}{2} \; k_B T \iint \tfrac{d^2 q_\perp dq_z}{(2\pi)^3} \; ln \left(K_1 q_\perp^4 + \mathcal{B} q_z^2\right). \quad (32)$$

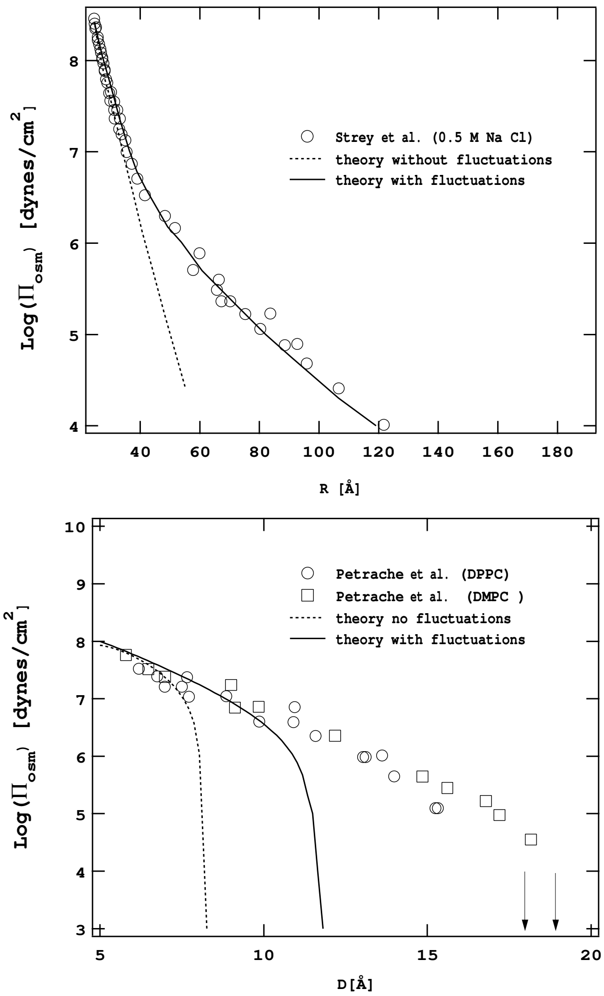

Figure 3. A fit of the lowest order fluctuation equations of state, Eqs. 27 and 34, to DNA [20] and lipid membrane [21] data. While for DNA theory and experiment essentially overlap, there is as yet no correspondence between them in the case of lipid membranes.

To evaluate the fluctuation part of the free energy I now proceed as follows. First I calculate

$$\frac{\partial \mathcal{F}}{\partial \mathcal{B}} = \frac{1}{2}\ k_B T V\ \ \iint \frac{q_\perp dq_\perp dq_z}{(2\pi)^2}\ \frac{q_z^2}{K_1 q_\perp^4 + \mathcal{B} q_z^2} = \frac{\pi k_B T V}{8\sqrt{K_1 \mathcal{B}}}\ \int q_z dq_z . \tag{33}$$

This integral depends again on the upper cutoff for $q_z = q_{z\ max}$. From here

I obtain the free energy in the form

$$\mathcal{F} \simeq \frac{\pi k_B T V}{8}\sqrt{\frac{\mathcal{B}}{K_1}}\; q_{z\ max}^2. \tag{34}$$

As before a meaningful cutoff for $q_{z\ max}$ would be proportional to the Brillouin zone radius $q_{z\ max} \simeq \frac{\pi}{D}$ where D is the average separation between the membranes in the stack. Again the mesoscopic elastic Hamiltonian has to break down below the scales set by $q_{z\ max}$.

In this case the osmotic compressibility modulus is taken in the form involving only the bare pair interactions between the molecules $U(\mathbf{r})$

$$\mathcal{B} \simeq V\frac{\partial^2 \mathcal{F}(D)}{\partial V^2} = D\frac{\partial^2 \mathcal{F}(D)/S}{\partial^2 D}, \tag{35}$$

where in this case $\mathcal{F}(D) = \mathcal{F}_{SR}(D) + \mathcal{F}_{vdW}(D)$ with D being the average first neighbor separation between the membranes in the array. Again we limit ourselves to the uncharged lipid membranes where the electrostatic term in the interaction is missing. For the bilayer bending rigidities we use the values obtained by Petrache *et al.* [21].

Surprisingly for a lipid membrane array the difference between the experiment and the theory on this level of approximation is still substantial, see Fig. 3. I interpret this difference as signifying that the compressibility modulus itself, and not just the osmotic pressure, has to be calculated by taking into account the thermal fluctuations. This is a much more ambitious project than the simple macroscopic elastic theory that appears to work for DNA. Let us see what we can do about it.

6. Fluctuation contribution to the compressibility modulus

At this point one can use any of the advanced theories that take into account the thermal fluctuations at a deeper level than the macroscopic theory of the previous section and that allow also for the thermal fluctuation effects on the value of the compressibility modulus itself [28]. Such theories are well worked out also in other areas of physics such as e.g. magnetic vortex arrays in type II superconductors. There are different approaches that one can follow. One could either formulate the problem in the language of the functional renormalization group [28] or on the level of a variational calculation of the compressibility modulus [29]. To remain as close as possible to the approach outlined before, we chose the second, *i.e.* variational, approach. It usually fares quite well even when compared to the more powerful renormalization group approach.

6.1. VARIATIONAL CALCULATION OF THE OSMOTIC PRESSURE: MULTILAMELLAR SYSTEM

I now improve on our estimate of the equation of state by evaluating the change in the osmotic compressibility not just osmotic pressure consistently for a fluctuating 2D multilamellar system. This was done first by Podgornik and Parsegian [30] and later by Nagle and coworkers [21]. In a multilamellar stack I assume that the interaction Hamiltonian can be written as:

$$\begin{aligned}\mathcal{H} \;=\; & \tfrac{1}{2}K_C\sum_{n=1}^{\infty}\int d^2\mathbf{r}_\perp \left(\boldsymbol{\nabla}_\perp^2 z_n(\mathbf{r}_\perp)\right)^2 \\ & +\tfrac{1}{2}\sum_{n=1}^{\infty}\int d^2\mathbf{r}_\perp \; V\left(z_{n+1}(\mathbf{r}_\perp) - z_n(\mathbf{r}_\perp)\right), \end{aligned} \tag{36}$$

where $z_n(\mathbf{r}_\perp)$ describes the local displacement of the n-th membrane in a stack in the z direction and $V(z)$ is the interaction potential between two neighboring membranes in a stack. I assume that the interactions are sufficiently short ranged that the next-to-first-neighbor interactions are negligible. Introducing the following parametrization of the local displacement

$$z_n(\mathbf{r}_\perp) = nD + u_n(\mathbf{r}_\perp) \qquad u_n(\mathbf{r}_\perp) = \sum_{\mathbf{Q},q_z} u\left(\mathbf{Q},q\right)e^{i\mathbf{Q}\mathbf{r}_\perp}e^{inDq_z}, \tag{37}$$

I define a harmonic reference Hamiltonian, the parameters of which will be evaluated variationally, in the form

$$\mathcal{H}_0 = \tfrac{1}{2}\sum_{\mathbf{Q},q_z}\left(K_C Q^4 + 4\mathcal{B}\sin^2\tfrac{q_z D}{2}\right)|u\left(\mathbf{Q},q_z\right)|^2 + V_0(D). \tag{38}$$

Evaluating the reference free energy with the help of $\mathcal{F}_0 = -kT\,\ln\left\langle e^{-\beta\mathcal{H}_0}\right\rangle$ I obtain

$$\mathcal{F}_0 = V_0(D) + \tfrac{kT}{2}\sum_{\mathbf{Q},q_z} ln\left(1+\frac{4\mathcal{B}\sin^2\frac{q_z D}{2}}{K_C Q^4}\right) = V_0(D) + \frac{kT}{2\pi D}\sqrt{\frac{\mathcal{B}}{K_C}}. \tag{39}$$

If I now compare the free energy of the exact Hamiltonian with the free energy of the trial Hamiltonian I have the Bogolyubov inequality $\mathcal{F} \leq \mathcal{F}_0 + \langle\mathcal{H}-\mathcal{H}_0,\rangle_0$, where the subscript 0 in the last term means that the average should be taken with respect to $\mathcal{H}_0$. The idea now is (Feynman - Kleinert [31]) to obtain an optimal upper bound for the free energy. This is obtained by treating $V_0(D)$ and $\mathcal{B}$ as variational parameters. Variation of the free energy in the Bogolyubov inequality with respect to these two parameters produces an optimal upper bound for the free energy. After defining

$$\sigma^2(\mathbf{Q},q_z) = \left\langle |u\left(\mathbf{Q},q_z\right)|^2\right\rangle = \frac{kT}{K_C Q^4 + 4\mathcal{B}\sin^2\frac{q_z D}{2}}, \tag{40}$$

and

$$V_{\sigma^2}(D) = \int dz\ V(z)\sum_{\mathbf{Q},q}\exp\left(iq(z-D) - \beta q_z^2\Delta^2\right), \tag{41}$$

where $V(\mathbf{Q},q)$ is the Fourier transform (wave-vector $\mathbf{k} = (\mathbf{Q},q)$) of the interaction potential Eq. 36, with

$$\Delta^2 = \sum_{\mathbf{Q},q}(1-\cos qD)\sigma^2(\mathbf{Q},q) = \frac{kT}{16K_C D\sqrt{K_C\mathcal{B}}}, \tag{42}$$

it is now straightforward to show that the variational equations for $V_0(D)$ and $\mathcal{B}$ can be obtained in the form

$$\begin{aligned}\mathcal{B}(1-\cos qD) &= \tfrac{1}{2}\tfrac{\partial}{\partial\sigma^2(\mathbf{Q},q)}V_{\sigma^2}(D)\\ V_0(D) &= \tfrac{1}{2}V_{\sigma^2}(D) - \mathcal{B}\Delta^2.\end{aligned} \tag{43}$$

The optimized free energy is given by its value in the reference system Eq. 39 with $V_0(D)$ and $\mathcal{B}$ calculated from Eq. 43.

When I compare the equation of state obtained from the free energy Eq. 39 I see a much better quantitative agreement with experiment, see Fig. 4. Obviously most of the thermal fluctuation effects have thus been taken into account. The same type of fit has also been carried out by Petrache *et al.* [21].

6.2. VARIATIONAL CALCULATION OF THE OSMOTIC PRESSURE: HEXAGONAL COLUMNAR SYSTEM

For a system with a hexagonal local symmetry I follow closely the calculation of Volmer and Schwartz [29] derived for the system of magnetic vortex line in type II superconductors. Apart from the difference between elastic energies of a vortex line vs. a flexible polymer the two cases are analogous. The interaction Hamiltonian of an oriented polymer array with hexagonal local symmetry can be written in the form

$$\begin{aligned}\mathcal{H} &= \tfrac{1}{2}K_C\sum_{n,m=1}^{\infty}\int dz\left(\frac{\partial^2\mathbf{r}_\perp{}^{(n,m)}(z)}{\partial z^2}\right)^2\\ &+\tfrac{1}{2}\sum_{n,m\neq n'm'}^{\infty}\int dz\ V\left(\mathbf{r}_\perp{}^{(n,m)}(z) - \mathbf{r}_\perp{}^{(n',m')}(z)\right),\end{aligned} \tag{44}$$

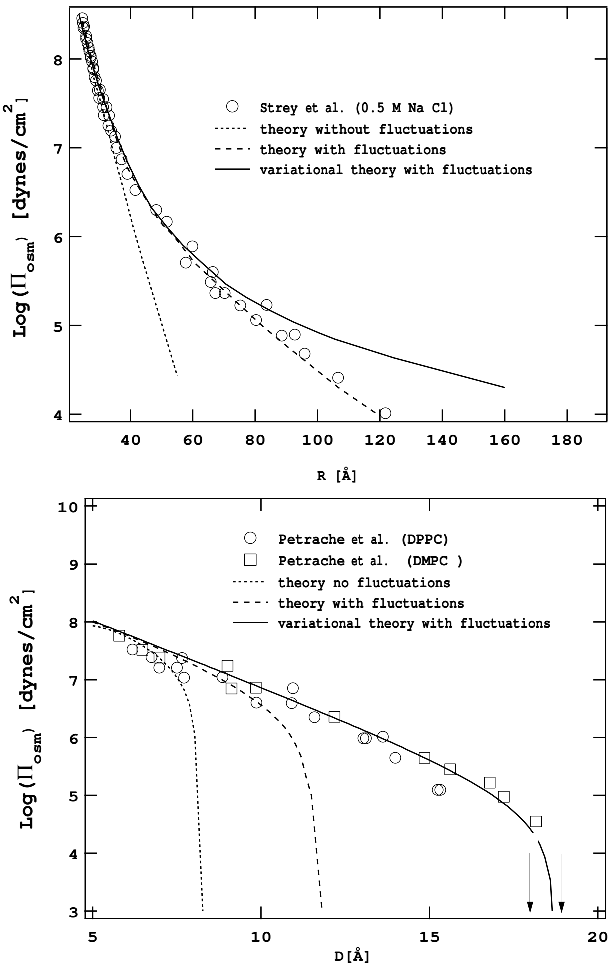

Figure 4. A fit of the variational equation of state obtained from Eq. 39 to the measured neutral lipid membrane array equation of state data [21], lower graph. The theory is now completely consistent with experiments. Surprisingly the same type of fit with a variational equation of state for DNA, upper graph, obtained from Eq. 50 fares much worse than the macroscopic fluctuation theory, see Fig. 3.

where $\mathbf{r}_\perp{}^{(n,m)}(z)$ is the local displacement of a polymer chain at the (n, m) lattice position perpendicular to the z axis. In principle the indices n, m would run through all the positions of the polymers at a certain planar cross section through the nematic but because of the short range nature of the interaction and computational convenience I restrict them to nearest neighbors [29]. Again instead of using this non-harmonic Hamiltonian I will take a simpler reference Hamiltonian of a general harmonic form. In the parameterization

$$\begin{aligned} \mathbf{r}_\perp{}^{(n,m)}(z) &= \mathbf{R}_{nm} + \mathbf{u}^{(n,m)}(z), \\ \mathbf{u}^{(n,m)}(z) &= \sum_{\mathbf{Q}_\perp, q_z} \mathbf{u}(\mathbf{Q}_\perp, q_z) e^{iq_z z + i\mathbf{Q}_\perp \mathbf{R}_{nm}} \end{aligned} \quad (45)$$

where $\mathbf{R}_{nm} = n\mathbf{a}_1 + m\mathbf{a}_2$, with $\mathbf{a}_1$ and $\mathbf{a}_2$ the two base vectors of the hexagonal lattice perpendicular to the long axis z of the molecules. I take the reference Hamiltonian in the harmonic form

$$\mathcal{H}_0 = \tfrac{1}{2} \sum_{\mathbf{Q}_\perp, q_z} \left(K_C q_z^4 \delta_{ik} + \mathcal{B}_{ik}(\mathbf{Q}_\perp) \right) u_i(\mathbf{Q}_\perp, q_z) u_k(-\mathbf{Q}_\perp, -q_z) + V_0(\mathbf{a}), \quad (46)$$

where $\mathcal{B}_{ik}(\mathbf{Q}_\perp) = \mathcal{B}_{ik} \sum_{\mathbf{a}} 4 \sin^2 \frac{\mathbf{Q}_\perp \mathbf{a}}{2}$ and the sum over $\mathbf{a}$ refers to summation over the positions of nearest neighbors. By exactly the same arguments as in the case of a multilamellar system I now derive an upper bound for the free energy corresponding to Eq. 44 *via* a variational estimate for the parameters in the reference Hamiltonian Eq. 46. Defining thus

$$\sigma_{ik}(\mathbf{Q}_\perp, q_z) = \langle u_i(\mathbf{Q}_\perp, q_z) u_k(-\mathbf{Q}_\perp, -q_z) \rangle = \frac{kT}{K_C q_z^4 \delta_{ik} + \mathcal{B}_{ik}(\mathbf{Q}_\perp)} \quad (47)$$

with

$$V_{\sigma_{ij}(\mathbf{Q}_\perp, q_z)}(\mathbf{a}) = \int d^2\mathbf{r}_\perp \; V(\mathbf{r}_\perp) \sum_{\mathbf{a}} \sum_{\mathbf{k}} e^{i\mathbf{k}(\mathbf{a} - \mathbf{r}_\perp) - 2\beta k_i k_j \sum_{\mathbf{Q}_\perp, q_z} \sin^2 \frac{\mathbf{Q}_\perp \mathbf{a}}{2} \; \sigma_{ij}(\mathbf{Q}_\perp, q_z)}, \quad (48)$$

the variational equations can be written in the form

$$\begin{aligned} 2\mathcal{B}_{ij} \sum_{\mathbf{a}} \sin^2 \frac{\mathbf{Q}_\perp \mathbf{a}}{2} &= \tfrac{1}{2} \frac{\partial V_{\sigma_{ij}(\mathbf{Q}_\perp, q_z)}(\mathbf{a})}{\partial \sigma_{ij}(\mathbf{Q}_\perp, q_z)} \\ V_0(\mathbf{a}) &= \tfrac{1}{2} V_{\sigma_{ij}(\mathbf{Q}_\perp, q_z)}(\mathbf{a}) - \tfrac{1}{2} \sum_{\mathbf{Q}_\perp, q_z} \mathcal{B}_{ik}(\mathbf{Q}_\perp) \; \sigma_{ij}(\mathbf{Q}_\perp, q_z) \end{aligned} \quad (49)$$

and the free energy can be obtained from

$$\mathcal{F}_0 = -kT ln \Big\langle e^{-\beta \mathcal{H}_0} \Big\rangle = V_0(\mathbf{a}) + \frac{kT}{2} \mathrm{Tr} \sum_{\mathbf{Q}_\perp, q_z} ln \left(\delta_{ik} + \frac{\mathcal{B}_{ik}(\mathbf{Q}_\perp)}{K_C q_z^4} \right). \quad (50)$$

Very similar equations have already been derived in the case of magnetic vortex arrays [29]. Though these equations look more complicated than in the multilamellar case, the only real difference between the two is the local symmetry of the assembly: lamellar vs. hexagonal columnar order.

However, when we compare the equation of state obtained from Eq. 50 with the one obtained from Eq. 27 we see that it fares much worse when compared with experiments or compared with the macroscopic fluctuation equation of state developed in section 4.1, see Fig. 4. This is surprising and demands an explanation.

The reason for this is found out to be quite simple. The variational *ansatz* with the bounded positional correlation function $\sigma_{ik}(\mathbf{Q}_{\perp}, q_z)$ fits best the description of a solid, with long range positional order. For a fluid, with only short range positional correlations, which is what the DNA array is at these densities, the positional correlations (as opposed to density correlations which of course remain finite) diverge in the thermodynamic limit and can not be described with a finite correlation function. Therefore the variational theory, strictly applicable only to a hexagonal crystal, fares much worse than the mesoscopic fluctuation theory of Section 4.1, if applied to a DNA array at densities between the crystalline and isotropic phases.

A variational theory similar in spirit to what I developed above was also put forth by de Vries [32] basing his analysis on previous work by Odijk [33]. Numerical results of this approach are indistinguishable from those presented above.

7. Interaction renormalization of the bending moduli

Until now we have studied the modification in the interactions between macromolecules wrought by their finite flexibility. The equation of state that we obtained for lamellar and hexagonal arrays contains also the material properties of the interacting macromolecules such as their mesoscopic elastic rigidities. In order to be consistent one also has to evaluate the effect of the interactions on those. We shall only consider the effect of long range intermolecular electrostatic interactions on the renormalization of the bending moduli.

7.1. LAMELLAR GEOMETRY

Let us do that first for the lamellar case that has been extensively reviewed by Andelman [14] and Fogden and Ninham [34]. The idea of these calculations is to solve the PB equation with non-planar boundaries and expand the corresponding electrostatic free energy in terms of the curvature of the boundaries.

Without going into formal details I will now list some of the main results dealing with the effect of the interactions on the bending rigidities in the case of a lamellar system. For a very thin membrane in the Debye-Hückel limit [14] one derives the change of the bending rigidity due to long range intramolecular interactions as [35]

$$K_C \longrightarrow K_C + \frac{3\,\sigma^2\lambda_D^3}{8\epsilon\epsilon_0} = K_C + \frac{3kT\lambda_D^3}{8\pi\ell_B b^2}, \tag{51}$$

where ℓ_B and the Gouy-Chapman length b have already been introduced in Sections 1.2 and 1.3. Note that electrostatic interactions on this level of approximation stiffen up the lipid membrane surface. This expression however works only for small surface charges *i.e.* in the linearized Debye-Hückel approximation. For higher charges, corresponding to the intermediate regime in Andelman's sense [14], the renormalized bending rigidity can be obtained in the form [36]

$$K_C \longrightarrow K_C + \frac{kT\lambda_D}{2\pi\ell_B}, \tag{52}$$

which can be derived heuristically from Eq. 51 by the substitution $b \longrightarrow \lambda_D$.

In the case of salt free, counterion-only limit the renormalization of the bending modulus is also dependent on the amount of space available for the counterions, *i.e.* to the interlamellar spacing, since the screening length scales as the amount of space available to counterions [3]. In the case of large surface charge density one is left with [37]

$$K_C \longrightarrow K_C + const. \frac{kTD}{\ell_B}, \tag{53}$$

where $const. = \mathcal{O}(1)$. On the other hand in the limit of low surface charge when the counterions behave almost as an ideal gas one derives [38]

$$K_C \longrightarrow K_C + const. \frac{kTD^3}{b^2\ell_B}. \tag{54}$$

If the surface charge density is high enough there is an additional effect that one has to realize when evaluating the electrostatic contribution to the bending modulus of a membrane. It stems from the ionic density correlations that can not be described on the level of the mean-field Poisson - Boltzmann theory.

Shklovskii and coworkers [39] have formulated a simple scheme, conceptually based on the Wigner crystal picture of a strongly correlated electron gas, to take these correlations into account for highly charged macromolecules where one can envision the counterions of valency Z as tightly associated with the macro molecular surface. In this case the electrostatic interactions decrease the bending modulus according to

$$K_C \longrightarrow K_C - const.\ kT\ Z^2 \left(\frac{\ell_B}{b}\right)\left(\frac{h}{b}\right)^2, \tag{55}$$

where h is the thickness of the membrane and $b = \left(2Ze/\sqrt{3}\sigma\right)^{1/2}$ is the average separation between the counterions of charge Ze_0 on the surface. Note again that the renormalized bending rigidity on this level of approximation gets smaller than the bare value.

This is however not the whole story. In a series of papers de Vries, see [40] and references therein, has explored the effect of thermal fluctuations in multilamellar systems in the salt free case for a much broader range of conditions than addressed here. Depending on the value of the Debye screening length, the separation between the bilayers and their surface charge he derived different regimes in the equation of state differing quite substantially in the role of the fluctuations. In the rather limited case treated here, corresponding to very low salt and relatively small interlamellar separations, the fluctuation and electrostatics in deed couple only through the renormalized bending rigidity and harmonic fluctuation theory.

7.2. CYLINDRICAL GEOMETRY

A similar roster of formulas can be assembled for the electrostatic renormalization of the bending modulus or equivalently the persistence length of a cylindrical macromolecule such as DNA in a hexagonal array [8]. In the case of low linear charge density of the macromolecule one has the famous Odijk-Skolnick-Fixmann [41, 42] result

$$K_C \longrightarrow K_C + \frac{kT\ell_B}{4(b\kappa)^2}. \tag{56}$$

In the case of high linear charge density, surpassing the Manning limit $b < \ell_B$, it is much more difficult if not impossible to obtain a closed formula for the persistence length renormalization. Different numerical estimates [43, 44] nevertheless allow for certain conjectures. For high enough salt and linear charge density above the Manning limit one can write

$$K_C \longrightarrow K_C + \frac{kT}{4\ell_B\kappa^2}. \tag{57}$$

It is generally believed that this formula captures the bending rigidity renormalization of DNA satisfactorily [45]. Recent experiments on stretching of single DNA molecules certainly corroborate this point of view [46, 47].

The above renormalized values for the persistence length are basically valid if the chain is very stiff to start with. In this case the chain stiffens up because upon bending the segments of the chain that were initially far apart get closer and since the interaction potential is repulsive it tends to stiffen up the chain. This mechanism of chain stiffening is usually referred to as "kinematic" stiffening.

If the limit of very stiff chain is no longer applicable, the renormalization of the persistence length is much more difficult to obtain and there is as yet no consensus emerging on what to expect. There have been several attempts ([48] and references therein) at evaluating the renormalized persistence length in different regimes defined by the elastic constant of the chain and the linear charge density of the chain, and what does transpire from these calculations is that the only parameter governing the behavior of the renormalized persistence length is $\mathcal{G}_0 = K_C\ell_B/kTb^2$. There still is disagreement on what exactly the different regimes are.

The most difficult regime to analyze is the small coupling regime defined by $\mathcal{G}_0 \ll 1$. For small enough $\mathcal{G}_0$ we argued [48] that one is first to encounter a regime of effective rigidities pertaining to very small bare elastic constants, *i.e.* the chain is originally very flexible, where the bending rigidity renormalization scales as

$$K_C \longrightarrow K_C + \left(\frac{K_C\ell_B}{kTb^2}\right)^{1/6}\left(\frac{kT}{K_C\kappa}\right)^{7/6}. \tag{58}$$

The persistence length renormalization in this case is not "kinematic" as is the case for high $\mathcal{G}_0$. Rather it is due to close proximity of different segments of the chain that are far apart along the chain. The mechanism of elastic modulus renormalization is thus completely different then in the Odijk-Skolnick-Fixman case. For even smaller values of $\mathcal{G}_0$ there is finally a regime described by

$$K_C \longrightarrow K_C + \left(\frac{K_C\ell_B}{kTb^2}\right)\left(\frac{kT}{K_C\kappa}\right)^{7}. \tag{59}$$

I should stress that these two regimes are obtained only at extremely (possibly, at least for DNA, unphysical) low values of the coupling parameter $\mathcal{G}_0$. Though there is wide consensus on the form of the persistence length renormalization in the OSF regime there is no similar consensus regarding the expressions for K_C in the low coupling regime.

In the salt free case there has been precious little work and reliable estimates are hard to obtain. Based on the numerical analysis of the solutions of the PB equation with counterions only [42, 43] one can conclude that the renormalized bending rigidity would in this case behave as

$$K_C \longrightarrow K_C + const.\frac{kT\ell_B R^2}{b^2}, \tag{60}$$

which for charges that surpass the Manning limit $b < \ell_B$ becomes

$$K_C \longrightarrow K_C + const.\frac{kTR^2}{\ell_B}. \tag{61}$$

Again as is usual for the salt free systems these equations can be interpreted as if the screening length would become of the order of the average separation R between the cylindrical molecules in a hexagonal array.

As in the case of planar macromolecules the effects of the counterion correlations show up also in the renormalization of the persistence length of cylindrical macromolecules. Shklovskii and coworkers [39] have evaluated the renormalization of the persistence length for tightly associated counterions of valency Z when they form a strongly correlated 2D liquid on and along the surface of the macromolecule. Their result is

$$K_C \longrightarrow K_C - const.\ kT\ Z^{7/2} \ell_B \left(\frac{a}{b}\right)^3, \tag{62}$$

where $b = \sqrt{2Ze/\sqrt{3}\sigma}$ is the average separation between the counterions on the surface and a is the radius of the cylinder. A limiting result for the renormalization of the persistence length was derived also by Hansen *et al.* [49] when the correlation contribution can be considered as a small perturbation to the mean field result. In this case one obtains

$$K_C \longrightarrow K_C + \frac{kT\ell_B}{4(b\kappa)^2} - \frac{kT}{12}\left(\frac{\lambda_D^3}{a^2}\right). \tag{63}$$

The second term on the r.h.s. is the OSF result and the next one describes the effect of correlations. Clearly in this limit the OSF and the correlation contributions are additive.

The form of the bending modulus renormalization thus obviously depends critically on the regime of counterion charge magnitude and salt concentration. Parts of the phase space of these variables, especially for cylindrical macromolecules have still remained unexplored especially those where the non-linear effects stemming from the Poisson - Boltzmann equation would presumably start to play a role [8].

8. Equation of state for salt free systems

In the case of salt free systems we have two different effects conspiring to rule out the fluctuations as a significant contributor to the total osmotic pressure. First of all it is the direct interactions between the macromolecules which are long ranged since for a salt free system the effective screening length is on the order of the average separation between the macromolecules, see Sections 1.2 and 1.3. Also the long range nature of the interactions makes the bending moduli depend on the average separation too, making them quite large (in the case that the correlation effects are negligible, *i.e.* if the counterions are monovalent) at sufficiently low density of macromolecules where the fluctuation effects should be highest, see Section 6.1 and 6.2. We will show how these two facts conspire to quench the effect of fluctuations on the equation of state. Without conformational fluctuations the equation of state is much easier to obtain than in the case of added salt where fluctuations play a prominent role.

The equation of state for both systems, hexagonal DNA arrays and multilamellar lipid membrane arrays, has been measured in nominally salt free conditions. For DNA the recent work by Raspaud *et al.* [50] and the old data by Auer and Alexandrowicz [51] cover a range of DNA densities spanning many orders of magnitude. The equation of state for charged lipids such as PG and PI at salt free conditions has been studies by Cowley *et al.* [53] and also provides a reliable set of data for gauging the accuracy of the theory, which is what we shall do in the next two sections.

8.1. LIPID MEMBRANE ARRAY

If we have only counterions with no additional salt the Poisson - Boltzmann equation can be solved analytically in a cell composed of an inner charged surface and an outer neutral surface where by symmetry the transverse component of the electrostatic field has to be zero [3]. A cell is thus composed of a charged surface with a fixed surface charge density σ and a symmetry surface at $z = D/2$ where the z-component of the electric field vanishes. This surface simulates the effects of the first neighbor at $z = D$. Solving the PB equation in a planar cell geometry one obtains for the osmotic pressure [3]

$$\Pi(D) = kT\ n(D/2) = \frac{kT}{2\pi l_B}\kappa^2(D), \tag{64}$$

where $\kappa(D)$ is the D dependent screening length, being the solution of

$$\kappa(D)D\ \tan\frac{\kappa(D)D}{2} = \frac{D}{b}, \tag{65}$$

and $n(D/2)$ is the concentration of counterions at the midpoint between the membranes, see Eq. 5. Eq. 65 can not be solved analytically but in two limiting cases as discussed in detail by Andelman [14]. In the ideal gas limit corresponding to $b \gg D$ and $\lambda_{DH} \gg D$, the limiting expression for the interaction free energy can be derived as

$$\mathcal{F}(D) = \frac{kT}{\pi\ell_B b}\ln DS. \tag{66}$$

In the Gouy-Chapman region however, which corresponds to $\lambda_{DH} \gg D$ and $b \ll D$, one remains with

$$\mathcal{F}(D) = \frac{\pi\ kT}{2l_B D}S. \tag{67}$$

Using now the form of the free energy for the salt free case (counterions only) Eqs. 66,67 and the renormalized values of the bending rigidities Eq. 54 (where I assume that in this case the largest contribution to the total bending rigidity comes from the electrostatic part which is evaluated in the low coupling limit) I can derive the magnitude of the fluctuation contribution, based on the theory developed in Sections 4.1 and 4.2. The following scaling forms valid in the lamellar geometry describe the fluctuation $\mathcal{F}_1$ and the bare contribution $\mathcal{F}_0$ to the total free energy of the system

$$\begin{aligned} \mathcal{F}_1 \sim \sqrt{\frac{\mathcal{B}}{K_C}} \sim D^{-5/2} \qquad vs. \qquad \mathcal{F}_0 \sim lnD \qquad\qquad (\text{small } \sigma), \\ \mathcal{F}_1 \sim \sqrt{\frac{\mathcal{B}}{K_C}} \sim D^{-2} \qquad vs. \qquad \mathcal{F}_0 \sim D^{-1} \qquad\qquad (\text{large } \sigma). \end{aligned} \tag{68}$$

The l.h.s. of the above comparisons corresponds to the magnitude of the fluctuation effects and the r.h.s. to the bare interactions, where the macromolecules are considered to be ideally rigid. Clearly for all values of the surface charge σ and sufficiently large D, the bare interactions are larger than the fluctuation modified interactions, in contrast to the case of screened electrostatic interactions. In the salt free limit the equation of state derived for an ideally rigid lattice should thus suffice.

One should again keep in mind however [40] that the above statements do not have universal validity and that the effect of the thermal fluctuations can have rather different consequences for a broader range of interlamellar separations, salt and surface charge then treated here. Especially in the case of low density surfactant systems the effects of thermal fluctuations are more complicated than alluded to above.

Numerical evaluation of the equation of state Eq. 64 compares well with experiments [53] performed on multilamellar arrays of salt free charged lipids PI and PG, if one adds a short range, hydration contribution Eq. 16 on top of the salt free electrostatics, see Fig. 5. We obtain a good fit if we assume there is one charge per $1400\,\text{Å}^2$ of the lipid surface. This is consistent with the amount of structural charge in the bilayers composed of egg PC, PG and PI. Thus the salt free equation of state Eq. 64 suffices for description of charged lipid data for most of the accessible macromolecular densities except close to molecular contact.

8.2. DNA ARRAY

If we have a salt free, *i.e.* counterion only, case for cylinders in an array with hexagonal symmetry the Poisson - Boltzmann equation can be solved analytically within the framework of the s.c. cell model [54]. A cell is composed of a single charged macromolecular cylinder of radius a and an outer

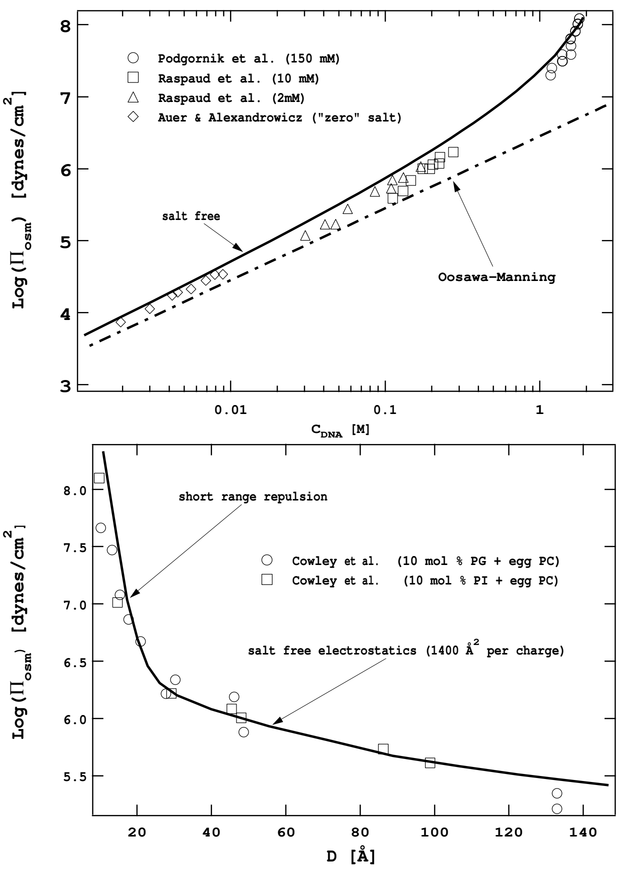

Figure 5. Equation of state for salt free DNA and lipid membrane array. Experimental data for DNA arrays in the medium, low and high densities are taken from [50], [51] and [52]. I have added the standard Manning - Onsager limiting law [55] for comparison. The salt free lipid data are taken from [53]. In both cases the simple equation of state for salt free systems, Eqs. 64 and 69, does a very good job in explaining the data for all but extremely large concentrations close to macromolecular contact.

cylindrical wall of radius $R/2$, simulating the effect of nearest neighbors at separation R, where by symmetry the radial component of the electrostatic field at the cell wall has to be zero. The Fuoss - Katchalsky - Lifson [54] solution leads to the following form of the osmotic pressure in the array [56]

$$\Pi(R) = kT\ n(R/2) = \frac{(1 + z^2(R))}{2\pi l_B\ R^2}, \tag{69}$$

where $n(R/2)$ is the concentration of counterions at the outer wall of the cell, where again by symmetry the electric field vanishes, and $z(R)$ is the solution of

$$ln(\frac{a}{R}) = \frac{\arctan\left(\frac{1-Q}{z(R)}\right) - \arctan\left(\frac{1}{z(R)}\right)}{z(R)}, \tag{70}$$

where $Q = \ell_B/\ell_{PO_4}$ is the dimensionless charge on the surface of the cylinder. a is of course the radius of the cylinder and ℓ_{PO_4} is the separation between the phosphate charges along the contour of DNA. Eq, 70 can not be solved analytically for general R.

One can however derive explicit dependence of the interaction free energy on the interaxial spacing between nearest neighbors R, in the limit of small and large R. It can be derived in the form

$$\mathcal{F}(R \longrightarrow \infty) \simeq \frac{kT\ L}{4\sqrt{3}\pi\ell_B}\ln\pi R^2, \tag{71}$$

and

$$\mathcal{F}(R \longrightarrow a) \simeq \frac{kT\ L}{4\sqrt{3}\pi l_{PO_4}}\ln\pi(R^2 - a^2). \tag{72}$$

The two free energies obviously have the ideal gas form (the ln of the space available to the counterions) with a different number of effective free particles per unit length of the macromolecules (note the change of $\ell_B \longrightarrow b = l_{PO_4}$, where $l_{PO_4} \sim 1.7\,\text{Å}$ is the separation between the phosphate charges along DNA [10, 49]), in the limit of large and small macroion concentrations.

Using these explicit limiting results we can now estimate the effect of fluctuations on the equation of state in a hexagonal array. If the interaction free energy is given by Eqs. 71, 72 then the renormalized bending rigidity is obtained from Eqs. 60, 61 leading to the following estimates

$$\begin{aligned}
\mathcal{F}_1 \sim \sqrt[4]{\frac{\mathcal{B}}{K_C}} \sim R^{-1} \qquad vs. \qquad \mathcal{F}_0 \sim ln\pi R^2 \quad (\text{small } \sigma), \\
\mathcal{F}_1 \sim \sqrt[4]{\frac{\mathcal{B}}{K_C}} \sim (R-a)^{-1} \qquad vs. \qquad \mathcal{F}_0 \sim ln\pi(R^2 - a^2) \quad (\text{large } \sigma),
\end{aligned} \tag{73}$$

and again the fluctuation terms are seen to scale with a larger negative power of R then the bare interactions, making them essentially irrelevant in the calculation of the equation of state. Again this runs in the opposite direction from the case of screened electrostatics where the fluctuation enhanced interactions are essential for understanding of the equation of state.

Evaluating $\Pi(R)$ for DNA one can quite successfully fit the measured equation of state [50, 51] in a very broad range of DNA densities with the structural parameters appropriate for the distribution of charge along DNA. Only at very high densities is there any discrepancy between the salt free calculated equation of state and the measurements, where the measurements decay faster with interaxial spacing than the electrostatic theory alone would predict. Again this is most probably due to the short range structural force kicking in at these high densities.

Comparing the measured and theoretical equations of state derived from Eq. 64 and 69 we see that they really describe the experiments performed in nominally salt free conditions quite well for all but extremely large macromolecular densities, see Fig. 5. Especially impressive is the case of DNA arrays where the theory and experiment match in a range of DNA densities spanning several orders of magnitude. Only at very large macromolecular concentrations corresponding to separations of a few Ångstroms before the contact do we see any noticeable deviation from theory.

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Index

Debye-Hückel limit, 22
DLVO interactions, 2
DNA, 1
DNA array, 1

elastic moduli, 13
equation of state, 1

forces between macromolecules, 4

Gouy-Chapman length, 7, 22

hexagonal array, 1
hydration interaction, 8

Interaction renormalization of the bending moduli, 1, 21

lamellar array, 9, 10

magnetic vortex arrays, 16, 20
membrane, 1
membrane array, 1
mesoscopic free energy, 12

Odijk-Skolnick-Fixmann result, 23
osmotic pressure, 1

Poisson-Boltzmann theory, 2

salt free systems, 25, 28

thermal fluctuations, 10

van der Waals interactions, 6–8

Wigner crystal, 22