Electrostatic Interactions in Mixtures of Cationic and Anionic Biomolecules: Bulk Structures and Induced Surface Pattern Formation

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Double Stranded DNA
2 chains each with -1 charge every base pair 3.4 Å
Diameter 20 Å
Persistence length (rigidity) of 500 Å (150 basepairs)
Hydrophilic (hides hydrophobic units)

Projection of the two phosphates on the double-helix axis gives linear charge density:
Double Stranded DNA: \(1 \text{ e} / 1.7 \text{ Å} \sim 6 \text{ e} / \text{nm}\)
(SHORT=rod; LONG=semi-flexible)
Single Stranded DNA: \(1 \text{ e} / 3.4 \text{ Å}\)
(flexible)

DNA is one of the most highly charged systems.
**Strong polyelectrolyte**

Synthetic example: Poly-Styrene-Sulphonate (100% S): \(1 \text{ e} / 2.5 \text{ Å} \sim 4 \text{ e} / \text{nm}\).
Persistence length 10 Å
Water soluble in monovalent salts at low ionic strength solutions.

Simple model:
charged chain (flexible, semiflexible or rod-like)
Solvated charge groups and ions
Water is structureless
Chains are stretched to decrease electrostatic repulsions

Flexible charged chains and counterions
DNA Condensation: precipitation occurs upon the addition of multivalent salt

- Metallic or organic 3+, 4+, higher multivalent salts (Cobalt hexamine, Spermine, Spermidine) precipitate DNA into toroidal bundles.
- Single stranded DNA and other flexible polyelectrolytes form compact structures.

Phase diagram: nearly universal

For
- Nucleosome core particles
- H1-depleted chromatine fragments
- short single-stranded DNA

DNA redissolution
In excess of spermine

Spermine Concentration (M)

DNA precipitation

DNA concentration (M)

(Raspaud et al., 1998-99)
Precipitation/condensation of polyelectrolytes

• Why do equal charges attract?

• The origin of the counterion driven attraction.

• Necessary elements to construct a theory.
Electrostatically driven self-assembly

• Cationic-Anionic Biological Complexes
  Viral assembly
  Chromosomes structure
  DNA packing for gene therapy
  Biotechnology (DNA condensation is used to increase DNA denaturation and cyclization rates by orders of magnitude as in vivo)
Virial Assembly: Helical and Sphere-like RNA Virus

(Tsuruta et al.)

Tobacco Mosaic Virus. One RNA (-) molecule of 6,300 base + 2,000 identical capsid (+) proteins

Self-assembles from capsid protein + viral RNA solution
Chromosome

Condensation Transition

DNA/ Histone electrostatic attraction versus Bending Stiffness.

Known structures

Nucleus: 23 chromosomes
Characteristic length for ionic dissociation/association in water:

The Bjerrum length $l_B$:

$$kT = \frac{e^2}{4\pi\epsilon\epsilon_0 l_B}$$

In water, $l_B = 7.14$ Å

if $d < l_B$ then ion pairing occurs

For a multivalent salt $z_i:z_j$

Association energy increases by $|z_i z_j|$ and $l_B \uparrow$
Simple salts

Potential at the arbitrary point $r$:

$$
\psi (r) = \int \frac{\rho(r')dr'}{4\pi\varepsilon\varepsilon_0|r-r'|}
$$

with $\rho(r)$ the total charge density at $r$

How does the charges distribution $\rho(r)$ change with respect to the distance $r$ from a central ion?
\[ \rho(r) \] is related to \( \psi(r) \) by the Poisson’s eq.,

\[ \Delta \psi(r) = -\rho(r)/\varepsilon \varepsilon_0 \]

If short range correlations are ignored (as in point ions), One can use the Boltzmann’s distribution,

\[ \rho(r) = z^+ e^+ e^{-z^+ \psi(r)/kT} + z^- e^- e^{-z^- \psi(r)/kT}, \]

The Poisson-Boltzmann (PB) equation. Expanding exponential gives linearized PB or Debye-Hückel (DH) theory:

\[
\Delta \psi = \begin{cases} 
0 & \text{if} \quad r < a \\
\kappa^2 \psi & \text{if} \quad r > a 
\end{cases}
\]

\[ \kappa^2 = \frac{4\pi l_B \rho^*}{a^3} = \frac{4\pi \rho^*}{a^2 T^*} \]

\[ T^* = a/l_B \]
Salt-free polyelectrolyte solutions, monovalent counterions

In polyelectrolytes the linearized theories are not valid. The chains are strongly perturbed by electrostatics.

\[ \xi \sim 1/\kappa^2 \approx (\rho^*)^{-1} \]

They are stretched due to the repulsions.

BUT ion association along the chains: Shape depends on how many ions are around the chains.
Non-linear effects in polyelectrolytes

- Start from the Poisson-Boltzmann equation
- BUT linearization is not possible because the approximation $z_i e \psi(r) \ll kT$ is not valid $\rightarrow$ ion pairing or ion condensation even at high $T^*$
In colloids the "condensed" ions renormalized the charge like a double layer in charged surfaces. Away from the macroion the interaction with other charges reflects only the effective charge of the macroion, and follows mean field values (Debye-Huckel, DVLO).

**Warning.** Poisson Boltzmann ignores short range correlations, which can be important in the dense ionic region or double layer.
Infinite rods the charge density in Bjerrum length $l_B$ units is

$$\xi = l_B / b$$

the Manning parameter

For B – DNA, $b = 1.7 \text{ Å}$:

$$\xi_M = 4.2$$

if $> 1/z_c$ ion condensation

**Monomers**

$z_m = -1$

**Counterions**

$z_c = +1$

« free » ions treated in the Debye-Hückel approximation.

« condensed » ions reducing the monomer charge to an effective charge $q_{eff}$. 
Counterion charge renormalization in 3D, only at finite concentration

(Alexander et al., 1984)

For charged spheres of size $R$, ion chemical potential far from the spheres, mainly entropic

$$kT \ln C,$$

on its surface, mainly enthalpic (electrostatic)

$$-q_{\text{eff}} e^2 / 4 \pi \varepsilon \varepsilon_0 R$$

$$q_{\text{eff}} \sim - R \ln C$$

The effective charge increases or the fraction of condensed ion decreases with dilution

For rods $R \sim N$ and the chemical potential $\ln N$ term
PB similar to equate chemical potential of free and condensed ions to determine the effective charge of the colloid. This can be done for any input charge distributions. For a fractal chains we input the distribution from the center of mass and allow the ions to “penetrate” the fractal.

\[ R \sim N^\nu \]
\[ \nu = 1 \text{ rod} \]
\[ \nu = 1/2 \text{ random walk} \]
\[ \nu = 1/3 \text{ dense ionic structure} \]
Conformation effects: fraction of condensed counterions (DH for ions only, no chain RPA contribution)

\[ q_{\text{eff}} \sim - R \ln C \]

(Gonzalez-Mozuelos & Olvera de la Cruz, 1995)
Poison-Boltzmann gives rod lowest energy though more ions are condensed in collapsed than in rod.

**IF SHORT RANGE CORRELATIONS**
as charge density increases or valence of counterions increases then collapse chains

Collapse to denser system of charges due to counterion induced attractions

Z=4.

Z=1.
Two-dimensional lattice of the multivalent counterions around the surface (Rouzina and Bloomfield 1996) and around rods (Arenson et al 1999, Solis and Olvera de la Cruz, 1999)

Correlation energy $\epsilon_c$ per ion $< 0$ (attractive)

If $n$: local concentration of the correlated liquid

$\epsilon_c \approx -W_c$

$\epsilon_c(2n) < \epsilon_c(n)$

Attraction between chains
In dense systems

Highly correlated ions leads to attractions (Modified D-H gives no transition in salt solutions)

$e^{-Kr}$ Repulsions only in dilute with point ions

(Brenner & Parsegian, 1972)

Ionic glass

(Solis + M.O. de la Cruz, 2000, 2001)
Phase diagram: nearly universal

DNA redissolution in excess of spermine

Spermine Concentration (M)

DNA precipitation

DNA concentration (M)

In the precipitated region the chains form an ionic crystal

(Raspaud et al., 1998-99)
Polyelectrolyte (PE) Chains in multivalent ions (Gonzalez-Mozuelos et al 95; Solis et al 00, 01; Lee + Thirumalia 00; Liu + Muthukumar 02))

**E. Luijten 04**

$\sigma_m \approx 2.5\text{Å};$ water at 298K: $l_B \approx 7.1\text{Å} \Rightarrow l_B / \sigma_m \approx 3; \ C_m = 0.008\sigma_m^{-3} \sim 1\text{M}$

$\text{PE}(N=32) + 8(4:1)\text{salt}$

**Scaling description:** $R_g \sim N^v$

- Charged rods (DD DNA) the precipitation is into bundles
- $\nu = 1/3$ sphere
- $\nu = 0.5$ ideal chain
- $\nu = 0.588$ coil
- $\nu = 1$ rigid rod
Effective charge

Polyelectrolytes collapse; beyond neutralization, re-expansion occurs because the multivalent ions can interact more with co-ions. Counterion size has crucial role.

Stability of complexes to segregation or to dissolution

Solis + MO de la Cruz 00, 01; Mesina, Holm and Kremer 00; Solis 02, Grosberg et al 02, Grosberg + Tanaka 01
Experiments on charge inversion,

Spermidine concentration ($Z_c = +3$)

No charge inversion

Spermine concentration ($Z_c = +4$)

Nucleosome Core Particles

(Raspaud et al., 1999; De Frutos et al., 2001)
Adsorption of Strongly Charged Polyelectrolytes onto Oppositely Charged Surface

Driving force: counterion release

Correlations along surface if distance between rods larger than adsorbed layer thickness (break down of PB) leads to charge inversion (Netz+ Joanny 99; Dobrynin+ Rubinstein 00).
Strongly charged rods in divalent solution

Polyelectrolytes adsorption onto same charged surfaces studied experimentally via X-Ray Standing waves (Libera, Cheng, Bedzyk).

Adsorbed rods via short range attractions
Time dependence of the Zn and Hg surface condensed layer coverages. The line is drawn to guide the eye.
Conclusions on precipitation

We have proposed a mechanism for attractions of purely electrostatic nature that describes the phase diagram.

Smaller multivalent ions are more efficient condensing polyelectrolytes. In order to observe re-dissolution by adding more multivalent ions one needs small association constants.

Mixture of mono and $z_c$-valent cations condensed onto the DNA induce non-universal phase diagrams

The non-ideal behavior of the “free” multivalent salt (determine by effective ionic sizes) reduced and may suppressed the DNA overcharging

Surface adsorption of polyions described by correlations.

Equal charge surface adsorption is possible via oppositely charged ions of valence 2+ (like – cell membranes to – DNA)
Peptide Amphiphiles (PA) nanofibers formed from acidic PAs by dropping the pH below 4.5 (low). Basic PAs self-assembled above pH 9 (middle).

Combining acidic and basic PAs at neutral pH self-assembly (top).

**Only form cylinders.** (S. Stupp lab for use as cell support such as laminin)
Multi-component micelles? (Solis, de la Cruz, Stupp 04)

Use oppositely charge units to built stable nano-aggregates with surface structure if units are otherwise immiscible.

Flat surface pattern due to the competition of surface tension $\gamma_0$ and charge density $\kappa$:

domain of size $L \sim A^{1/2}$ is $L \sim (\gamma_0/\kappa^2)^{1/2}$

The fraction of area $f$ of one unit in the cell of area $A$ determines the pattern structure.
\[
\frac{F}{A} = \frac{\gamma}{L} s_1 + \frac{1}{2} \sigma^2 L s_2
\]

\[
A_o = \frac{\gamma}{\sigma^2}
\]

The phase diagram in 2D looks like this:

\[f_c = 0.35, 0.65\]
Pure Coulomb $F \sim L$
Screened $F \sim L, L<1/\epsilon$ or $F \sim 1/\epsilon$, $L>1/\epsilon$

Macrophase segregation

Homogeneous

Hexagonal

Full segregation
Electrostatics generate multicomponent micelles and vesicles with surface patterns.

With screening the domain size jumps from finite to macroscopic segregation.
MONTE CARLO EQUAL SIZE AND OPPOSITE CHARGE

+1 and -1

Sort range = 3KT

Electrostatic $1/\varepsilon \sim 0.1$

Conclusion: in two dimensions one can create periodic patterns using the competition among electrostatic and van der Waals interactions