Supplemental Information for Designing Electrostatic Interactions via Polyelectrolyte Monomer Sequence

Tyler K. Lytle,† Li-Wei Chang,‡ Natalia Markiewicz,¶ Sarah L. Perry,*‡§ and Charles E. Sing*,¶∥

†Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana IL, USA
‡Department of Chemical Engineering, University of Massachusetts Amherst, Amherst MA, USA
¶Department of Chemical and Biomolecular Engineering, University of Illinois at Urbana-Champaign, Urbana IL, USA
§Institute for Applied Life Sciences, University of Massachusetts Amherst, Amherst MA, USA
∥Beckman Institute, University of Illinois at Urbana-Champaign, Urbana IL, USA

E-mail: perrys@engin.umass.edu; cesing@illinois.edu

Monte Carlo Simulation

Monte Carlo simulations were performed for systems containing \( n_{P^-} \) homopolyanions, \( n_{P^+} \) patterned polycations, \( n_{S^+} \) cations, \( n_{S^-} \) anions, and water using the restricted primitive model; this is identical to the model considered in our previous work on charge patterning.¹ The water solvent was modeled as a continuum with relative dielectric constant \( \epsilon_r = 78.5 \). Nonsolvent species were modeled as hard spheres, with charged species having a diameter
Figure S1: Schematic of restricted primitive model system. The polyanion chains are homopolymers with every monomer charged and colored blue. The polycation chains copolymers of charged monomers, orange, and neutral monomers, white. The size of the neutral monomers is bigger than in the actual system for visual clarity. Cations are red, and anions are purple. Charged beads have a diameter $\sigma_\pm$, and neutral monomers have a diameter $\sigma_0$. Charged species interact with each other through a Coulomb potential, $U_{ES}$. Polymers are bound together with a bonding potential, $U_B$, and have a bending potential, $U_\theta$. 
σ± = 4.25 Å and neutral monomers in the polycation chain having a diameter σ0 = σ±/4. Polymeric species have a degree of polymerization N, and polycations have a charge fraction, \( f_C \), which is the number of charged monomers divided by the total degree of polymerization. Schematically this is represented in Figure S1. The total potential of the system is given by:

\[
U = U_{ES} + U_{HS} + U_B + U_\theta
\]  
(S1)

where \( U_{ES} \) is the electrostatic potential, \( U_{HS} \) is the hard sphere potential, \( U_\theta \) is the bending potential, and \( U_B \) is the bonded potential. The electrostatic potential is a Coulomb potential given by:

\[
U_{ES} = \sum_i \sum_{j>i} \frac{q_i q_j e^2}{4\pi \varepsilon_0 \varepsilon_r r_{ij}}
\]  
(S2)

In this equation, \( q_i \) is the valency of bead \( i \), \( e \) is the charge of an electron, \( \varepsilon_0 \) is the vacuum permittivity, and \( r_{ij} \) is the separation between beads \( i \) and \( j \). Electrostatic interactions are calculated using Ewald summation. The beads have excluded volume captured via a hard-sphere potential:

\[
U_{HS} = \sum_i \sum_{j>i} \left\lbrace \begin{array}{ll}
\infty & r_{ij} < \left(\frac{\sigma_i}{2}\right) + \left(\frac{\sigma_j}{2}\right) \\
0 & r_{ij} \geq \left(\frac{\sigma_i}{2}\right) + \left(\frac{\sigma_j}{2}\right)
\end{array} \right.
\]  
(S3)

Polymeric species are bound together using a square-well bonding potential:

\[
U_B = \sum_i \left\lbrace \begin{array}{ll}
\infty & r_{i,i+1} < \Delta_{\text{min}} \\
0 & \Delta_{\text{min}} \leq r_{i,i+1} \leq \Delta_{\text{max}} \\
\infty & r_{i,i+1} > \Delta_{\text{max}}
\end{array} \right.
\]  
(S4)

where \( \Delta_{\text{min}} \) is the minimum bond length, and \( \Delta_{\text{max}} \) is the maximum bond length. The polymers also have some stiffness modeled using a bending potential as a function of the
angle between two connected bonds, $\theta_{i,i+1,i+2}$, given by:

$$U_{\theta} = \sum_i \frac{\kappa}{2} (\theta_{i,i+1,i+2} - \theta_0)^2$$ (S5)

where $\kappa$ determines the strength of the angle potential, and $\theta_0$ is the equilibrium angle between adjacent bonds.

These simulations used degree of polymerizations $N=48$ or 50, depending on the charge sequence of the polycation. Maximum and minimum bond lengths were set at $\Delta_{\text{min}}=\sigma_{\pm}$ and $\Delta_{\text{max}} = \Delta_{\text{min}} + 0.01 \sigma_{\pm}$. The angle potential strength is set at $\kappa = 3.30 k_B T$, where $k_B$ is Boltzmann’s constant, and $T = 298$K is the temperature. The equilibrium angle is $\theta_0 = 0$.

Monte Carlo Simulations of a Single Polyelectrolyte in Dilute Salt Solution

The above Monte Carlo model was used to determine the localization of salt ions near a single polyelectrolyte in a dilute salt system, represented schematically in Figure S2. A single polyelectrolyte was simulated with salt ions to determine the number density $n_C(s)$ of condensed salt ions as a function of monomer index $s$. During the simulation, the separation distance between monomers and salt ions were calculated. If this separation was within a cutoff distance, $r_c = 1.5 \sigma_{\pm}$, then the salt ion was considered to be localized at the monomer. An additional simulation was performed in the limit of no electrostatic interactions, and the number density of condensed salt ions $n_{C,0}(s)$ was again calculated. The ratio of these two numbers was used to calculate the monomer-dependent energy parameter $\epsilon(s)$. These simulations were performed using $\phi_S = 1.32 \times 10^{-4}$, which was taken to be sufficiently large that the polymer counterions represented only a small fraction of the overall number of salt ions in the system. We show two representative simulation snapshots in Figure S3 for charged (left) and uncharged (right) polymers.
Figure S2: Schematic of the single chain Monte Carlo simulations. The polycation has orange beads representing charged monomers and white beads representing neutral monomers. Anions are purple, and cations are red. These simulations measure the number density of condensed counterions as a function of monomer index. A counterion is considered condensed if the separation between the counterion and monomers is less than a cutoff distance $r_c$. This cutoff distance is schematically represented as the dashed, green circle.
To determine the value of $\epsilon(s)$, we use a simplified expression for $n_C(s) \sim e^{-(\epsilon(s) - \mu)/(1 + e^{-(\epsilon(s) - \mu)})}$ that is based on a simple, uncorrelated adsorption of counterions along a chain backbone. This approximates the value of $\epsilon$ as implicitly including the many-body interactions associated with the local chain environment in the simulation (i.e., nearby monomers). This expression for $n_C$ is dependent on the value of the chemical potential $\mu$ in this simple adsorption description, so we also ran MC simulations in the absence of electrostatic interactions to obtain a related $n_{C,0}(s) \sim e^\mu/(1 + e^\mu)$. This number is non-zero, since there is always some concentration of opposite salt ions in the cutoff radius $r_C$. The ratio of these two number densities is $n_C/n_{C,0}(s) = \exp(-\epsilon(s))$ in the limit that $e^\mu \sim \phi_S \ll 1$, which is true at low salt concentrations.\textsuperscript{1} To show that this procedure is, in this limit, insensitive to the choice of salt concentration, we show the value of $\epsilon(s)$ plotted for a wide range of concentrations (spanning $\approx 1.5$ orders of magnitude in $\phi_S$) in Figure S4. We plot sequences A and C, along with the homopolyanion used in this manuscript, and emphasize that there is excellent agreement in $\epsilon(s)$ among the different values of $\phi_S$. 

Figure S3: Snapshots of single-molecule simulations of sequence D used to determine $\epsilon(s)$, including simulations with charged (left) and uncharged (right) polymers.
Figure S4: Monomer-dependent energy $\epsilon(s)$ as a function of the chain index $s$, measured by single-polyelectrolyte simulations over a range of dilute salt concentrations $\phi_S$. Sequences A and C are considered, along with the corresponding homopolyanions, and exhibit nearly identical values of $\epsilon$ regardless of the choice of $\phi_S$. 
**Molecular Dynamics Simulations**

Snapshots shown in Figure 2b were taken from molecular dynamics simulations using the above-described restrictive primitive model with alterations to the excluded volume and bonding potentials so that they are no longer discontinuous. Excluded volume is included in these simulations using a Lennard-Jones potential \( U_{LJ} \) given by:

\[
U_{LJ} = \sum_i \sum_j 4\epsilon_{LJ} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] \quad r_{ij} < r_{ij}^c
\]

\( \epsilon_{LJ} \) is the depth of the potential well, \( \sigma_{ij}^{LJ} \) is the separation between beads \( i \) and \( j \) at which this potential becomes 0, and \( r_{ij}^c \) is the cutoff distance for \( U_{LJ} \). The square-well bonding potential is replaced with a harmonic spring potential:

\[
U_B = \sum_i \frac{\kappa_B}{2} (r_{i,i+1} - r_0)^2
\]

where \( \kappa_B \) is the bond potential strength, and the equilibrium bond distance is \( r_0 \).

The bonding potential parameters are set as \( \kappa_B = 250k_B T \) and \( r_0 = 1.05\sigma_\pm \). The hard sphere potential is matched by setting the Lennard-Jones parameters as \( \epsilon_{LJ} = 10.75k_B T \) and \( \sigma_{ij}^{LJ} = r_{ij}^c = (\sigma_i + \sigma_j)/2 \). Pair correlation functions were calculated for a number of concentrations of polymer and salt to show that the structure of MD and MC simulations match almost exactly.\(^2\)

### Pressure Calculation

Pressure, \( p \), was calculated using phantom box volume changes\(^3\) in Monte Carlo simulations with no salt ions. For each instance of calculating pressure both a compressive and expansive volume change is performed. These volume changes have the same magnitude, but different directions. Since these are phantom volume changes, the volume of the simulation box does
not change throughout the simulation. Pressure can be calculated via:

\[
p\frac{\Delta V}{k_B T} = (Nn_{P+} + Nn_{P-}) \ln \left(1 + \frac{\Delta V}{V}\right) + \ln \left\langle \exp\left(-\frac{\Delta U}{k_B T}\right)\right\rangle \\
- \ln \left\langle \exp\left(-\frac{\Delta U}{k_B T}\right)\right\rangle
\]  

(S8)

Here \( V \) is the volume of the box. \( \Delta V_i \) is the size of the volume change, and \( i \) denotes the direction of the volume change, with + being expansive and − being compressive. \( \Delta U_i \) is the change in potential energy due to the volume change, \( i \). The first term on the right hand of Equation S8 is the pressure due to an ideal gas of monomers. The second and third terms are the monomer excess pressure, but the desired quantity is the chain excess pressure. This quantity allows thermodynamic integration to yield the excess free energy.

To accomplish this, we use arguments found in K.G. Honnell, et al. \(^4\) The monomer excess pressure, \( p_{\text{EXC}}^m \), is defined as:

\[
p_{\text{EXC}}^m = \ln \left\langle \exp\left(-\frac{\Delta U}{k_B T}\right)\right\rangle - \ln \left\langle \exp\left(-\frac{\Delta U}{k_B T}\right)\right\rangle
\]  

(S9)

As the concentration approaches 0, the intermolecular forces should become negligible, which means the pressure should approach the value for an ideal gas of chains. For this to be true, Equation S9 has to approach \( \{(n_{P+} + n_{P-}) k_B T/V\} - \{(Nn_{P+} + Nn_{P-}) k_B T/V\} \) in this limit. If this expression is subtracted from equation S9, then the chain excess pressure, \( p_{\text{EXC}}^c \), is recovered:

\[
p_{\text{EXC}}^c = \ln \left\langle \exp\left(-\frac{\Delta U}{k_B T}\right)\right\rangle - \ln \left\langle \exp\left(-\frac{\Delta U}{k_B T}\right)\right\rangle \\
- \{(n_{P+} + n_{P-}) k_B T/V\} - \{(Nn_{P+} + Nn_{P-}) k_B T/V\}
\]  

(S10)

This excess pressure can be used to calculate excess free energies.
Figure S5: Phase diagrams for the investigated patterns. The $2\Phi$ region is the immiscible part of the phase diagram, and the $1\Phi$ region is the miscible part of the phase diagram. (a) Simulation phase diagrams calculated using equation S12. We note that sequence E did not exhibit phase separation in simulation. (b) Theoretical phase diagrams calculated using the transfer matrix theory. The letters corresponding to each phase diagram denote the pattern in Figure 1d. Both simulation and theory show alterations in phase behavior as charge fraction and the average length of the run of charged monomers is changed.

The excess free energy per volume can be defined as:

$$f_{EXC} (\{\phi_i\}) = \frac{F_{EXC} (\{\phi_i\})}{V k_B T} = \phi_P \int_{\phi_S, \phi_P}^{\phi_S^0, \phi_P^0} \frac{V F_{EXC}^{c} (\phi_S^0, \phi_P^0)}{N_{pat} k_B T \phi_P^0} d\phi_P^0$$

$$+ \int_{\phi_S^0, \phi_P}^{\phi_S, \phi_P} \mu_{EXC,S} (\phi_S', \phi_P') d\phi_S'$$

(S11)

where $N_{pat} = f_C n_{P+} N + (1 - f_C) n_{P+} N (\sigma_0/\sigma_\pm)^3 + n_{P-} N$. $\phi_i^0$, with $i = S$ for salt and $i = P$ for polymer, is the reference volume fraction, which we set to 0, and, $\mu_{EXC,S}$ is the salt chemical potential, calculated via Widom insertion of a pair of salt ions.\(^5\) This excess free energy can be used as an input into a total free energy expression:

$$\frac{\mathcal{F}}{V k_B T} = \sum_i \frac{\phi_i}{N_i} \ln \phi_i + f_{EXC} (\{\phi_i\})$$

(S12)
The first term on the right hand side of this equation is the mixing entropy of all species, and the second term is the simulation-calculated excess free energy. This free energy can be used to calculate phase diagrams, shown in Figure S5 for patterns A-J as described in Figure 1d.

Comparison of these phase diagrams with those contained in previous work from the authors reveals some differences. We attribute the discrepancy to the different techniques used to calculate the excess free energy. Previously, the excess free energy was calculated via:

\[ f_{\text{EXC}}(\{\phi_i\}) = \int_{\phi_S^0,\phi_P^0}^{\phi_S^0} \mu_{\text{EXC},P}(\phi_S^0, \phi_P^0) \, d\phi_P^0 + \int_{\phi_S^0,\phi_P^0}^{\phi_S^0} \mu_{\text{EXC},S}(\phi_S^0, \phi_P) \, d\phi_S^0 \]  

(S13)

Here, excess chemical potentials are calculated for the polymer using incremental Widom insertion. In order to adapt this technique to the patterned polycation, the pattern is shifted along the polymer backbone to capture the contribution of the charged and neutral monomers to the excess chemical potential. This resulted in phase diagrams with a larger polymer concentration in the supernatant phase compared to the current results. However, both techniques qualitatively capture the observed patterning trends.

**Peptide Synthesis**

Polypeptides with were prepared using standard Fmoc-based solid-phase synthesis on a Liberty Blue automated microwave peptide synthesizer from CEM, Ltd. using methods reported previously. Briefly, peptides were synthesized on a Rink amide MBHA resin (Peptide Solutions) using Fmoc-L-Lys(Boc)-OH, Fmoc-D-Lys(Boc)-OH, Fmoc-L-Glu(tBu)-OH, Fmoc-D-Glu(tBu)-OH, and Fmoc-Gly-OH (Peptide Solutions, LLC). 20% Piperidine (Sigma Aldrich) in N,N-dimethylformamide (DMF, sequencing grade, Fisher BioReagents) was used for Fmoc deprotection, while 0.5M N,N-diisopropylcarbodiimide (DIC, 99% Acros Organics) and 1M ethyl (hydroxyimino)cyanoacetate (Oxyma, Peptide Solutions) in DMF were used...
as activator and base, respectively. Cleavage from the resin and side-chain deprotection was performed in 95/2.5/2.5 trifluoroacetic acid (TFA, Fisher)/water (MilliQ 18.2 MΩ·cm, Millipore)/triisopropylsilane (98% Acros Organics) for 3 hours at room temperature. The resulting peptides were precipitated into cold anhydrous ethyl ether (BHT stabilized, Fisher Scientific). The final product was characterized by matrix-assisted laser desorption/ionization time of flight mass spectrometer (MALDI-TOF, Bruker UltrafleXtreme).

Poly(glutamate) with degree of polymerization $N = 50$ was synthesized using amino acids of alternating chirality (D and L) to mitigate inter-peptide hydrogen bond formation.$^{1,8-10}$ Similarly, all patterned poly(lysine-co-glycine) peptides were synthesized using amino acids of alternating chirality (D and L), with the exception of sequences A-C. Lysine peptides are present as TFA salts, while glutamate has a sodium counterion.

**Preparation of Stock Solutions**

Polypeptide stock solutions were prepared gravimetrically using Milli-Q water at a concentration based on the total number of amino acids present. For instance, a stock solution of the homopolyanion poly(glutamate) of 10 mM amino acid would be used in parallel with a stock solution of a half-charged poly(lysine-co-glycine), also at 10 mM with respect to the total number of amino acids, or 5 mM with respect to the number of charged monomers present in solution. All solutions were adjusted to pH = 7.0 ±0.03 using concentrated solutions of HCl and NaOH, as needed. Monomer concentration was chosen as the experimental basis in order to easily enable direct stoichiometric comparison of the number of positively and negatively charged units present in solution.

Sodium chloride (NaCl) was purchased as a powder from Sigma Aldrich. A stock solution was prepared gravimetrically at 0.5 M and adjusted to pH = 7.0, as above.
Coacervate Preparation

Complexation was performed using stoichiometric quantities of positively and negatively charged polypeptides at a total charged residue concentration of 1 mM at pH 7.0. Under these conditions, it is a reasonable approximation to describe all of the residues on both polypeptides as fully charged. Samples were prepared by first mixing a concentrated solution of NaCl with MilliQ water in a microcentrifuge tube (1.5 mL, Eppendorf), followed by the polyanion. The resulting mixture was then vortexed for 5 s before addition of the polycation. The final mixture was vortexed for at least 15 s immediately after the addition of polycation to ensure fast mixing. The resulting phase separation causes the sample to take on a cloudy, or opalescent appearance, due to the formation of small droplets of the complex coacervate phase.

Determination of Salt Resistance \( (c_{S,E}^0) \)

Samples were examined using brightfield optical microscopy (EVOS XL Core, Fisher Scientific) to determine the 'salt resistance' \( (c_{S,E}^0) \), or the salt concentration above which no phase separation occurs. All samples were imaged within 1 h of preparation. Error bars on measurements of the salt resistance correspond to the salt concentration intervals over which samples were examined.

Salt Resistance \( (c_{S,E}^0) \) versus Critical Salt Concentration \( (c_S^0) \)

In this paper, we simultaneously use salt resistance \( c_{S,E}^0 \) as the experimental measure and the critical salt concentration \( c_S^0 \) as the theoretical/computational measure of the strength of electrostatic interactions and thus coacervation. These values represent different parts of the phase diagram, and therefore have different numerical values. The motivation to use
Figure S6: The values of the critical salt concentration $c_0^S$ versus the salt resistance $c_0^{S,E}$ for theoretical predictions of the entire set of sequences considered in this manuscript. We demonstrate a linear correlation between these values, except at the lowest $c_0^S$, where the binodal is always $c_p > 1$mM.
Figure S7: The values of the salt resistance $c_{S,E}^0$ for (a) simulation predictions and (b) experiment for sequences A-D. We note that, for our parameterization scheme, these exhibit reasonable numerical matching. We note that this measurement is not precise for simulation, motivating our use of $c_S^0$ in the main manuscript.

different values stems from practical or theoretical challenges in each method:

**Experimental** efforts rely on solid-phase synthesis of polypeptides, which produce small quantities of highly-precise, sequenced polymers that also have a relatively short degree of polymerization $N \approx 50$. The limits on the amount lead to practical challenges in characterizing the entire coacervate phase diagram, where the critical point for these polymers is predicted to be at rather high polymer concentrations $c_P \approx 100 - 500$ mM. Instead, we find the location of the binodal at much lower polymer concentration of $c_P = 1$ mM where less overall polymer material is required, providing the value of $c_{S,E}^0$ used in the manuscript.

**Simulation** determination of the binodal uses thermodynamic integration (described earlier) to calculate the phase diagram. To perform this calculation, a discrete number of simulations were carried out at regularly spaced salt/polymer concentrations, where excess chemical potentials and pressures were calculated. Polynomial surface fits to these discrete data points were used in the integration, over the entire range of $c_P$ and $c_S$. While we numerically observe that these fits provide an excellent description of the free energy landscape, the low end of the binodal is expected to be the most sensitive to the nature of this fit due to its dependence on only a few of the original discrete simulations. As we will show
later, we are still able to obtain excellent qualitative agreement with trends and even nearly quantitative agreement with experimental observations. We expect the critical salt $c_{S}^{0}$ to be a more robust measure of the overall free energy landscape and consequent phase diagram we obtain.

**Theoretical** determination of the binodal is limited by the assumptions in the transfer-matrix theory. A major assumption, outside the local arrangement of correlated charges that is described by the ion-pairing in the adsorption picture, is that the local environment of the polymer and salt species is well-described by a mean field. This type of assumption is known to be inaccurate, due to the existence of ‘paired’ polyelectrolytes at low $c_{P}$; here, the local concentration of the oppositely-charged polymer is significantly enhanced over the mean field prediction. In our model, this manifests as a difference in the effective translational entropy of the polymer; in the mean-field approximation, each polymer exhibits full translational degrees of freedom, while the established presence of paired complexes in the dilute regime would result in each pair exhibiting full translational degrees of freedom. This means that the theory, while qualitatively capturing the same competition between translational entropy in the supernatant and pairing energy and entropy in the coacervate, slightly over-predicts the $c_{S}$ location of the dilute-branch of the binodal at a given $c_{P}$. This effect is significant in the region for which $c_{S,E}^{0}$ is used, motivating our use of the critical salt concentration $c_{S}^{0}$ as a more accurate metric that is seen in Figure 2 of the main manuscript to match well with simulation predictions.

While the values $c_{S,E}^{0}$ and $c_{S}^{0}$ are numerically different, we can demonstrate that these values are both highly correlated. We plot in Figure S6 both values for the theoretical phase diagrams, for which we have the most data for both $c_{S,E}^{0}$ and $c_{S}^{0}$. While there is not a one-to-one numerical matching (which is not expected), we do demonstrate that there is an extremely linear correlation so long as the binodal passes below $c_{P} = 1$ mM. Therefore, trends in one value correspond *directly* to trends in the other.

We can further demonstrate that the parameterization that we use for simulation and
theory predicts phase diagrams that are numerically similar to the experimental observations. This is slightly obscured by the use of $c_{S,E}^0$ versus $c_S^0$, which we motivated in the preceding paragraphs. To demonstrate this connection, we plot the value of $c_{S,E}^0$ for both simulation and experiment in Figure S7. We note, as previously discussed, that the values of $c_{S,E}^0$ for simulation are not predicted to be as precise as $c_S^0$. Nevertheless, the numerical values are similar to those obtained in experiment.

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