Contents lists available at ScienceDirect



Advances in Colloid and Interface Science

journal homepage: www.elsevier.com/locate/cis

Development of the modern theory of polymeric complex coacervation



Charles E. Sing *

Department of Chemical and Biomolecular Engineering, University of Illinois at Urbana-Champaign, 600 S. Mathews Ave. Urbana IL, 61801, United States

ARTICLE INFO

ABSTRACT

Available online 29 April 2016 Keywords: Polyelectrolytes Coacervation Polymer physics Electrostatics Complexation Oppositely charged polymers can undergo the process of complex coacervation, which refers to a liquid–liquid phase separation driven by electrostatic attraction. These materials have demonstrated considerable promise as the basis for complex, self-assembled materials. In this review, we provide a broad overview of the theoretical tools used to understand the physical properties of polymeric coacervates. In particular, we discuss historic theories (Voorn–Overbeek, Random Phase Approximation), and then describe recent developments in the field (Field Theoretic, Counterion Release, Molecular Simulation, and Polymer Reference Interaction Site Model methods). We provide context for these methods, and map out the patchwork of theoretical models that are used to describe a diverse array of coacervate systems. We use this review of the literature to clarify a number of important theoretical challenges remaining in our physical understanding of complex coacervation.

© 2016 Elsevier B.V. All rights reserved.

Contents

1. Introduction	. 2
2. Complex coacervates versus polyelectrolyte complexes	. 3
3. Historical theory development	. 3
3.1. Voorn–Overbeek model	. 3
3.2. Random Phase Approximation	. 4
4. Modern approaches to complex coacervation	. 6
4.1. Experiments and the need for new complex coacervate theories	. 6
4.2. The complexation approach	. 7
4.3. The field theory approach	. 9
4.4. The simulation approach	. 10
5. A unified theory of complex coacervation?	. 11
6. Conclusion	. 13
Acknowledgments	. 13
References	. 13

1. Introduction

Charged polymeric materials have a long and established history in the field of polymer science [1,2]. Understanding how the presence of Coulombic interactions affects long chain molecules remains a vibrant field of research [3,4], which is relevant to almost every field of polymer science. Indeed, for fields such as polymers for energy materials [5,6] and the physics of biological macromolecules [7–11] an understanding of charges is foundational. Theoretical challenges persist in the field of polymer electrostatics that have motivated their study for decades [12]. In particular, there is a convergence of a wide array of length scales; Coulomb interactions are long-range, and often compete with molecular interactions at short length scales [12]. This leads to competitions between steric, electrostatic, and entropic considerations that are challenging to describe both theoretically and conceptually.

An emerging class of materials that embodies these longstanding challenges in polymer electrostatics are systems known as 'polymeric complex coacervates' [8,10,13–17]. Coacervates consist of oppositely charged species that assemble in an aqueous solution, typically with a high concentration of salt (0.1–4 M) [13–19]. While any number of charged species can form these assemblies, including proteins,

^{*} Tel.: +1 217 244 6671.

E-mail address: cesing@illinois.edu.

surfactants, and colloids [15,19,20] [21], we will focus in this review on polymer-based coacervates. These mixtures undergo a liquid–liquid phase separation, where one phase is polymer dilute and the other is polymer-rich (Fig. 1a) [13,16]. The polymer-rich phase is essentially a transient gel, with the oppositely charged polymers forming temporary, electrostatic crosslinks.

The utility of complex coacervate materials is well established. Originally studied by Bungenberg de Jong and Kruyt in biomacromolecular systems of proteins and polysaccharides [13], coacervates have been used as additives [8,22,23] in food processing and personal care products as encapsulants [24,25], emulsifiers [26], and viscosity modifiers [27]. This motivated the initial forays into coacervate study [23], and has inspired progress using biomacromolecules useful for food science [8,13-15,22-30]. Recently, however, oppositely charged soft materials (including both polymers and colloidal particles) have emerged as a powerful motif in material self-assembly [17,31-41]. Complex coacervation has been used to drive ordered block copolymer gels [32,33,35, 41], stimuli-responsive sensory materials [31], and coacervate-core micelles useful for drug delivery [17,34,35,37,39,40,42]. The study of complex coacervation has now returned to its roots in biological materials, with analogues to coacervation found in underwater adhesives [10, 43–46], membrane-less organelles [47], and even proto-cells meant to reproduce the fundamental aspects of living systems [48–50].

The renaissance of work in polymeric complex coacervation has inspired the development of new theoretical tools to understand the physical state of these systems. This review is intended to provide an introduction to the broader field of complex coacervation theory both as it currently stands as well as its historical development. Indeed, this progress has been intimately tied to progress in the theory of polyelectrolytes as a whole, and while the intent is that this article is a standalone introduction to coacervation we point readers to a number of reviews focusing on modern and historical developments in polyelectrolyte physics that complement the current review [3,4,12].

2. Complex coacervates versus polyelectrolyte complexes

Introduction of coacervate theory first requires an important discussion of what physically 'constitutes' a complex coacervate. This is hardly trivial, and is still an area of active inquiry [51]. Complex coacervates are often considered to be either a subset of or distinct from a class of materials known simply as 'polyelectrolyte complexes'. Indeed, there is a significant amount of ambiguity in the field as to the difference between these two materials, and early theoretical papers will sometimes treat the two systems as interchangeable [52–54].

In this review, we will consider the theory for both complex coacervates and polyelectrolyte complexes as limiting cases of the same

Coacervation

a)

underlying physical interactions. However we suggest a distinction; for polymers, complex coacervates are stable, aqueous, and liquid-like phases of oppositely charged polyelectrolytes where there is no 'oneto-one' exclusivity between the chains. In other words, each chain interacts with *multiple* other polyelectrolyte chains that may be dynamically replaced by other chains in observable time scales. Polyelectrolyte complexes, alternatively, typically refer to systems that do not meet all the criteria necessary to be a coacervate. For example, complexes are sometimes considered a polyelectrolyte phase where the charge attractions drive the system to be kinetically arrested [51,55–58]. We will distinguish these systems as non-equilibrium complexes. Alternatively, complex is also commonly used to refer to pairs of oppositely charged chains that exclusively interact in an infinitely-dilute medium [59-68]. We will call these soluble complexes [69]. Both non-equilibrium and soluble complexes share a key characteristic that distinguishes them from coacervates; there is little ability for chains to 'replace' each other on observable time scales. This is due either to kinetic trapping or to the absence of nearby chains. Both types of complex are similarly relevant to a number of applications. Non-equilibrium complexes are integral to layer-by-layer assembly [58,70-73], while soluble complexes are used for a number of drug delivery technologies that utilize complexation between DNA and polycations [67,68,74].

These three classes of materials: coacervates, soluble complexes, and non-equilibrium complexes, have been historically developed using the same few theoretical insights that lead to a comprehensive picture of polyelectrolyte complexation and coacervation. We will revisit the distinctions throughout the review, but will also note the connections among this broad spectrum of materials.

3. Historical theory development

 c_{S}

Soluble Complex

Non-equilibrium complex

3.1. Voorn-Overbeek model

Bungenberg de Jong and Kruyt first described coacervation in the late 1920s when they observed the formation of dense liquid droplets from a series of biomolecular species such as casein, serum albumin, tannin, and gelatin [13]. It was determined that polymeric coacervates consisted of four non-water species: a polyanion, a polycation, a cation, and an anion [13]. Mixtures of these species were observed to undergo a phase separation under certain conditions into a polymer dense and a polymer dilute phase [13]. These early experimental results represent underlying observations that persist across most manifestations of coacervation [13].

This initial work prompted the development of a theoretical framework to describe coacervate systems [16,28,75]. Voorn and Overbeek published the first successful theory of complex coacervation in 1957

2Φ

1Φ



b)

[16,75]. Their model was investigated over a series of articles by them and others [16,28,75,76], and demonstrated that qualitative matching and/or quantitative fits can be achieved using a relatively simple model based on the Flory–Huggins theory of polymer mixing and the Debye–Hückel theory of simple electrolytes [16,75]. Both of these theories provide analytical expressions for the free energy associated with their respective subjects [2,77]. The Flory–Huggins theory predicts the mixing of a polymeric species with a small molecule solvent [2], which Voorn and Overbeek used to describe both the polycation and polyanion in water. The Debye–Hückel theory offers a limiting expression for the free energy associated with dilute, weakly interacting electrolytes [77,78]. These were identified as both the charges on the salt species (both the cation and anion) as well as the charges along the backbone of the polycation and polyanion chains. The resulting free energy expression over the species i= +, -, P+, P-, S is [16,18,28,75]

$$\frac{a^{3}F}{Vk_{B}T} = \sum_{i} \frac{\phi_{i}}{X_{i}} \ln \phi_{i} + \sum_{i} \sum_{j>i} \chi_{ij} \phi_{i} \phi_{j} - \alpha \left[\sum_{i} \sigma_{i} \phi_{i}\right]^{\frac{3}{2}}$$
(1)

The first two terms are generalized Flory–Huggins contributions, written in terms of the volume fraction of all the species ϕ_{i} , the Flory χ_{ij} -parameter between species *i* and *j*, and the polyelectrolyte degree of polymerization X_i . The last term corresponds to the Debye–Hückel free energy. This includes the combined concentration of charges, using a stoichiometric coefficient σ_i to relate charge concentration to ϕ_i . The strength of the electrostatic interactions $\alpha = \frac{e^2}{8 \pi \epsilon_0 k_B T} = \lambda_B/2a$ is the dimensionless Bjerrum length $\lambda_B = e^2/(4\pi\epsilon\epsilon_0 k_B T)$, which represents the distance over which the electrostatic energy is larger than the thermal energy $k_B T$ [3,4,78].

The properties of this theory have been widely studied, in particular in the plane of salt concentration versus polymer concentration [16,18, 19,34,75,79–81]. Fig. 1b demonstrates a schematic of a phase diagram typical from calculating the appropriate equilibrium conditions ($\mu_i^{\alpha} = \mu_i^{\beta}$) for a binodal curve defining a two-phase coexistence region (between a polymer-rich α phase and polymer-deficient β phase) at low salt and polymer concentrations [18]. Indeed, this is the region where 'coacervation' occurs due to liquid–liquid phase separation.

Extensions to the Voorn–Overbeek theory have been developed to consider coacervate systems that do not match well with the original predictions of Voorn–Overbeek theory. For example, Veis et al. incorporated a reaction scheme of aggregating soluble complexes, in an attempt to explain the apparent entropic nature of coacervation in experimental phase diagrams [28]. Work by Tainaka extended this scheme to understand the role of excess polyions [76].

This formalism has persisted as the primary way to describe complex coacervation, either as a way to describe data in the experimental literature or to provide the conceptual framework within which experimentalists consider complex coacervate systems. Examples of the former are present throughout the literature, including a number of recent results [18,19,34,79-82]. Spruijt et al., for example, experimentally determined the entire binodal curve for a number of molecular weights [18]. Three fit parameters in Voorn–Overbeek were parameterized: the charge density σ_i , which indicates the stoichiometric ratio of monomers to polymerized charges, the size of the charges a that determines the strength of the electrostatic interactions α , and finally the γ_{ii} parameter that captures dispersive interactions [18]. Judicious choice of these parameters led to a direct correspondence between the experiment and the theory, for both the binodal as well as the water content of the coacervate (Fig. 2a) [18]. Similar matching can be found in other predictions stemming from Voorn-Overbeek. For example, Qin et al. used a Helfand-Tagami approach to calculate the scaling of surface tension as the salt concentration c_s approached its critical value c_s^0 [83]. They calculated a result $\gamma \sim (1 - \frac{c_s}{c_s^0})^{3/2}$ that indeed matches with experiment (Fig. 2b) [79].

3.2. Random Phase Approximation

Due in large part to the apparent success of the Voorn–Overbeek model [18], efforts to improve on its predictions and its sophistication have progressed in parallel with the Flory–Huggins theory upon which it is based. The Edwards approach to polymer field theory led to a general framework to systematically consider mean-field theories and include fluctuations [84–86]. For coacervates, the partition function \mathcal{Z} for a system of polymers is reframed in the context of a path integral:

$$\mathcal{Z} \sim \prod_{j}^{n_{P+},n_{P-}} \int \mathcal{D}\boldsymbol{r}_{j} \prod_{k}^{n_{C+},n_{C-}} \int d\boldsymbol{r}_{k} \prod_{l}^{n_{S}} \int d\boldsymbol{r}_{l} \exp\left(-\beta U_{0}\left[r^{2n_{P}N}\right] - \beta U_{1}\left[r^{2n_{P}N+2n_{C}+n_{S}}\right]\right) \\ -\beta U_{2}\left[r^{2n_{P}N+2n_{C}+n_{S}}\right] \delta\left(\sum_{i}\hat{\rho}_{i}-\rho_{0}\right)$$
(2)

This is a Canonical partition function for n_{P+} polycations, n_{P-} polyanions, n_{C+} cations, and n_{C-} anions in n_S solvent molecules. Densities are given by operators $\hat{\rho}_{S}$, $\hat{\rho}_{C\pm}$ and $\hat{\rho}_{P\pm}$ that give the density at a spatial location **r**. The script $D\mathbf{r}_i$ indicates the integral is over all *paths* (i.e. configurations and conformations) that a series of polymers may take. All of these interact via a version of the 'Edwards Hamiltonian' that energetically constrains the trajectory of the polymers through space as a function of the segment index *s* (i.e. the number of segments along the chain contour): $\beta U_0[\mathbf{r}^{2n_pN}] = 3/2a^2 \sum_j^{2n_p} \int_0^N ds \left| \frac{d\mathbf{r}_j(s)}{ds} \right|^2$. Also included in the Hamiltonian are dispersive χ -interactions $\beta U_1[\mathbf{r}^{2n_pN+2n_c+n_s}] =$ $(\nu_0/2)\int d\mathbf{r} \sum_{ij} \chi_{ij} \hat{\rho}_i(\mathbf{r}) \hat{\rho}_j(\mathbf{r})$ (where ν_0 is a solvent/polymer unit volume), and the electrostatic interactions $\beta U_2[\mathbf{r}^{2n_pN+2n_c+n_s}] = (\lambda_B/2)$ $\int d\mathbf{r} \int d\mathbf{r} \hat{\rho}_E(\mathbf{r}) \hat{\rho}_E(\mathbf{r}') / |\mathbf{r} - \mathbf{r}'|$. This includes the charge density operator, $\hat{\rho}_E = \hat{\rho}_{C+} + f \hat{\rho}_{P+} - \hat{\rho}_{C-} - f \hat{\rho}_{P-}$, where *f* is the fraction of charged segments. The delta function in Eq. (2) constrains the polymer and solvent densities to equal the average system density at all points. The above integral can be recast as an integral not over the paths of the polymers and the possible positions of all the ions, but rather as an integral over the density fields of the five species $\phi_i = \phi_{P+1}, \phi_{C+2}, \phi_S$ their respective chemical potential fields $\mu_i = \mu_{P\pm}, \mu_{C\pm}, \mu_S$, and an electrostatic potential field ψ :

$$\mathcal{Z} \sim \int \mathcal{D}\phi_i \mathcal{D}\mu_i \mathcal{D}\psi \mathcal{D}\eta \exp(-\beta \mathcal{H}[\phi_i, \mu_i, \psi, \eta])$$
(3)

Here, a Lagrange multiplier field η has also been introduced to maintain $\sum_i \phi_i = 1$. The Hamiltonian $\mathcal{H}[\phi_i, \mu_i, \psi, \eta]$ for coacervates has the form [87,88]:

$$\beta \mathcal{H}[\phi_{i},\mu_{i},\psi,\eta] = -n_{P\pm} \ln Q_{P\pm}[\eta,\mu_{P\pm},\psi] - n_{S} \ln Q_{S}[\eta,\mu_{S}] - n_{C\pm} \ln Q_{C\pm}[\eta,\mu_{C\pm},\psi] + \rho_{0} \int d\mathbf{r} \left[\frac{1}{2} \sum_{i,j} \chi \phi_{i}(\mathbf{r}) \phi_{j}(\mathbf{r}) + \eta(\mathbf{r}) \left(\sum_{i} \phi_{i} - 1 \right) - \sum_{i} \mu_{i}(\mathbf{r}) \phi_{i}(\mathbf{r}) + \sum_{i} q_{i} \phi_{i}(\mathbf{r}) \psi(\mathbf{r}) - \frac{|\nabla \psi(\mathbf{r})|^{2}}{8\pi \lambda_{B}} \right]$$

$$(4)$$

There are five components $i = P \pm , C \pm , S$ representing the polyelectrolytes, counterions, and solvent respectively. Q_i are the single polymer/particle partition functions, evaluated by considering all the configurations and conformations of each species in their respective fields (combinations of μ_i , ψ , and η). The electrostatic potential field ψ interacts with the components with charge q_i , and itself has energy given by the final term in the Hamiltonian.

There is a connection between Eq. (4) and standard Flory–Huggins theory. In the case of a polymer solution, there is an absence of counterions and charges on the polymers, there is only one polymer species, and a homogeneous state (e.g. $\phi_i(\mathbf{r}) = \langle \phi_i \rangle$) is considered. This last assumption signifies a mean-field theory, and is the sole contributing term in the integral in Eq. (3). Using $F = -k_B T \ln Z$ this simplifies to



Fig. 2. (a) Experimental determination of complex coacervate binodal curve for a number of chain lengths of poly(acrylic acid) and poly(N,N-dimethylaminoethyl methacrylate) (left) [18]. Similarly, the fraction of water in the coacervate is also measured for each point along the right side of the binodal (right) [18]. All curves demonstrate excellent fits to the Voorn–Overbeek theory, upon appropriate choice of fit parameters α , σ , and χ (Spruijt et al.) [18]. Reprinted with permission from Spruijt, E, et al. Macromolecules 2010;43:6476–6484. Copyright 2010 American Chemical Society. (b) Voorn–Overbeek theory can be used to calculate the expected scaling of the normalized surface tension γ/γ_0 as the critical salt concentration ψ_c is approached (curve), which matches experimental data (points) [79]. Reprinted with permission from Qin, J, et al. ACS Macro Lett. 2014;3:565–568. Copyright 2014 American Chemical Society.

Flory–Huggins theory for the free energy F_{MF} . In particular, the first two terms lead to the entropic contribution (the first term in Eq. (1)), and the first bracketed term is the enthalpic contribution (the second term in Eq. (1)).

The full Eq. (3) can be also evaluated using a homogeneous meanfield assumption ($\phi_i(\mathbf{r}) = \langle \phi_i \rangle$) to yield the analogue to Flory–Huggins for coacervate-forming systems. The resulting free energy *does not* predict coacervation, however; the last term would trivially give zero contribution due to the lack of field gradients, and the only other difference is the presence of a counterion entropy term. In general, this theory is only non-trivial (1) at interfaces when electroneutrality can be broken and (2) in equilibrium coexistence where the ideal gas entropy of the counterions is the primary influence on phase equilibria. Voorn– Overbeek theory surpasses this result by incorporating the Debye– Hückel result around a test charge [52,77]. By doing so, Voorn–Overbeek therefore incorporates some fluctuations around the mean-field result. Thus, the Random Phase Approximation (RPA) is historically invoked to include these fluctuations more systematically.

While the approximation of a homogeneous state as the main contributor to the partition function only leads to a modified Flory–Huggins theory, the formalism provides a way to systematically extend the theory to include increasing numbers of fields in the partition function. RPA does this by expanding in fluctuations around the homogeneous fields (all fields are in the form $\phi_i(\mathbf{r}) = \langle \phi_i \rangle + \delta \phi_i(\mathbf{r})$) [87,89]. By converting to Fourier space, $\delta \phi_i(\mathbf{r}) = (2\pi)^{-3} \int d\mathbf{k} \, \delta \phi(\mathbf{k}) \exp(-i\mathbf{k} \cdot \mathbf{r})$, it is possible to write the partition function in the form:

$$\mathcal{Z} \sim \exp(-\beta F_{MF}) \int \mathcal{D}\delta\phi_i \mathcal{D}\delta\mu_i \mathcal{D}\delta\psi \mathcal{D}\delta\eta \exp\left(-\frac{\beta}{2} \int \frac{d\mathbf{k}}{(2\pi)^3} \Omega_i(\mathbf{k}) M_{ij}(\mathbf{k}) \Omega_j(\mathbf{k})\right)$$
(5)

where $\Omega_i = (\delta \phi_j, \delta \mu_j, \delta \psi, \delta \eta)$ is a vector that represents the various field variables and $M_{ij}(\mathbf{k}) = (\delta^2 \mathcal{H} / \delta \Omega_i \delta \Omega_j)$. The starting point for RPA includes the fluctuations as deviations from mean-field theory up to the *second* order (see schematic in Fig. 3a) [89]. This is therefore a Gaussian integral that can be solved. This can be performed for all non-density field variables to yield an equation that is the starting point for most RPA-based analysis [52,53,87,89–91]:

$$\mathcal{Z} \sim \int \prod_{i} \mathcal{D} \delta \phi_{i} \exp\left(-\frac{\beta}{2} \int \frac{d\boldsymbol{k}}{(2\pi)^{3}} \delta \phi_{i}(\boldsymbol{k}) S_{ij}^{-1}(\boldsymbol{k}) \delta \phi_{j}(\boldsymbol{k})\right)$$
(6)

where the matrix S_{ii}^{-1} is the inverse structure factor.

The inverse structure factor, for RPA, provides information on the deviations from mean-field behavior. Each wave vector k sets a length scale, and the structure factor denotes how important these length scales are to the deviations from the mean-field free energy. This occurs through spatial correlations, either from particle interactions (such as electrostatic interactions) or from chain connectivity interactions. Positive values of the structure factor indicate an increase in free energy, and at k = 0 the distances are associated with *macroscopic* values of *r* and thus represent thermodynamic stability. Thus, these tools are used in a number of ways. For example, the free energy can be directly evaluated for a given phase by calculating the full partition function, or the stability of the phase is considered based on the sign of the inverse structure factor at k = 0. Higher-order terms can be systematically included, forming the foundation of field theoretic models that have had a profound role in treating both polymer systems [84,91-93] and electrostatic systems [94–97]. In particular, the RPA model for electrolytes is related to Debye-Hückel theory, and thus serves as the basis to systematically improve field theoretic models of coacervation [52].



Fig. 3. (a) Field theory approaches consider density fields $\{\phi_i\}$ that determine the Hamiltonian \mathscr{H} and thus the partition function $\mathscr{Z}_{-}\int \mathcal{D}\phi_i \exp(-\beta\mathscr{H})$. We schematically illustrate the various levels of evaluating this partition function. The mean-field approximation considers only a single field configuration (the minimum of $\mathscr{H}, \mathscr{H}^*$) to contribute to \mathscr{Z} . The RPA considers fluctuations to second order (Gaussian fluctuations). Full field theoretic approaches sums over all fields, which typically must be performed numerically. (b) Extensions of RPA for complexes by Castelnovo and Joanny were used to calculate phase behavior, with the dependence of the polymer concentration in the complex \tilde{c} on the overall charge concentration $\tilde{n} + f\tilde{c}$ [171]. Reprinted with permission from Castelnovo M and Joanny J-F. Langmuir 2000;16:7524–7532. Copyright 2000 American Chemical Society. (c) Kudlay and Olvera de la Cruz extended this approach to account for the finite size of the charges, leading to a similar phase diagram of the polymer concentration ϕ_s (top) [53]. Importantly, the excess salt $\phi_s^D - \phi_s$ is plotted (bottom) to demonstrate that salt is expelled from complexes at high salt concentrations, in contrast with Voorn–Overbeek predictions [53]. Reprinted with permission from Kudlay A, Olvera de la Curz M. J. Chem. Phys. 2003;120:404. Copyright 2003, AIP Publishing LLC.

RPA and related approaches have been used to tackle both complexation (in the framework of Lifshitz–Grosberg globule theory) [98], multilayer formation [73], as well as complex coacervation [52]. Initial work on these systems led to a variety of behaviors. For example, the phase diagram of a complex was determined as a function of salt and solvent quality, and extension to coacervates was postulated due to a precipitation of globular complexes [98]. Coacervates themselves require the one-loop approximation (an extension of RPA that modifies S_{ij}^{-1} to reflect how it changes due to density fluctuations), leading to predictions that can (for example) bridge standard Flory–Huggins-based ternary mixtures and complex coacervation by adjusting the strength of dispersive versus electrostatic interactions [52].

Castelnovo and Joanny developed this one-loop RPA-based model of complexes, which dissolve as the salt concentration is increased (Fig. 3b), yielding predictions for a number of charge monomer fractions [52]. They also discuss the limitations of these methods [52]. Indeed, density fluctuations due to chain correlations couple to the electrostatic correlations; however, they note the limitations of this method as the charge density gets large and discuss a need for an 'ion pair' approach [52]. Similarly, the finite sizes of the charges are not explicitly considered; the Hamiltonian only implicitly includes this in the entropic mixing term, which is based on the mixing of species whose volume fractions sum to 1. These weaknesses were partly addressed in followup papers from Kudlay, Ermoshkin, and Olvera de la Cruz, who explicitly included the finite size of the ions by modifying the Coulombic potential and diagrammatic expansions that consider strong local effects due to ion complexation and van der Waals attractions [53,54]. This strategy furthermore addresses the issues of high-k (small r) divergences in standard RPA approaches. This work yields similar results, however this demonstrates that for most conditions the finite size of the charges depletes them from the complex (Fig. 3c).

Ultimately, RPA and related analytical field theory approaches elucidate the physical couplings between chain connectivity and electrostatics, and can introduce corrections to account for excluded volume and correlation effects [53,54]. These are highly sophisticated theories, yet their sophistication limits both their adaption by experimentalists and the transparency of their assumptions. Indeed, there are well-known challenges with regard to both electrostatics and polymers treated in RPA and related perturbative approaches [94]. In particular, such theories do not converge when the electrostatic interactions are strong or the ion valency is large [94]. This is an important limitation; high charge densities along a polymer chain remain a challenge because multivalent ions are in the limit of high charge densities. Approaches to circumvent these challenges have been widely proposed for polyelectrolyte systems, typically relying on the supposition of an alternate 'highly-ordered' state such as an ionic solid [99,100], effective chi-parameters [101,102], and/or ion condensation [103–106]. While motivated by strong physical intuition, these invoke assumptions about the system that decreases their predictive power or limits their regime of applicability. Nevertheless, these understandings have been instrumental in progressing the state of complex coacervation.

4. Modern approaches to complex coacervation

4.1. Experiments and the need for new complex coacervate theories

There has been a recent resurgence in the experimental study of complex coacervation. Many of the motivations that have previously spurred interest in coacervates remain, such as their utility in cosmetics and food additives [22], however new applications have come to the forefront. For example, the connection between complex coacervates and the origins of life is an old idea, but recent work has begun to develop 'proto-cells' that take advantage of the biology-like environment of complex coacervates [48–50]. This connection has found utility in tissue engineering applications [107,108]. Biological analogues with membrane-less organelles and underwater adhesives have also been investigated extensively [10,43–47]. Beyond biology, charge complexation has found use as a powerful motif in self-assembly. Layer-bylayer assembly has seen applications ranging from fuel cell membranes to coatings for drug delivery [58,70–72,109–112]. Block copolymers can form coacervate-core micelles useful for drug delivery and protein encapsulation [17,32,34,37,39,40,42,69], or stimuli-responsive photonic materials and gels [31,33,41].

Almost all of these applications for coacervation or complexation require further theoretical development due to specific challenges not addressed by Voorn–Overbeek or RPA theoretical frameworks. For example, layer-by-layer assemblies are often in kinetically trapped states (which can be desirable for the function of devices made using this method) [71,72,109,110], and block copolyelectrolyte features exist over a large spectrum of length scales [12]. Biological systems and analogues also often possess features such as stiff macromolecules [113] and specific interactions such as hydrogen bonding [56,114] that extend beyond electrostatic and dispersive interactions typically considered in classical coacervation theories.

Recently, fundamental experimental work has continued to probe the physical properties of complex coacervates [18,20,44,51,56,79,80, 115-118]. This work includes mixed success when Voorn-Overbeek and RPA results are considered. Perhaps the strongest success is captured by the work of Spruijt et al., which compares experimental phase diagrams in the salt concentration/polymer concentration space with the phase diagram calculated from Voorn-Overbeek theory [18]. This matching data is parameterized by the strength of the χ -parameter as well as the linear charge density, which are treated as adjustable parameters [18]. Appropriate choice of parameters leads to excellent fits to experimental data over a broad range of chain lengths [18]. This has motivated the use of Voorn-Overbeek theory to study coacervate interfaces, with similar matching to experiment. Despite this success, Voorn–Overbeek has fallen short in a number of situations. For example, recent work has demonstrated that the identity of a salt ion is important to the equilibrium phase behavior of a coacervate [81,115], and this is not predicted by Voorn–Overbeek, and tellingly is related to the Hofmeister series of ions [115,119,120]. It has been demonstrated that charges are often expelled from the coacervate (the opposite is true of Voorn-Overbeek) [121], and that coacervation is primarily an entropic process (i.e. not strongly driven by enhanced electrostatic attraction) [118]. Finally, molecular features such as hydrogen bonding and chirality are known to have significant affects [56], including the tendency to form kinetically trapped 'precipitates' that are not hydrated systems.

Mismatches between Voorn–Overbeek predictions and experimental results are expected, because the range of applicability of its assumptions is often far outside where it is used. In particular, the Debye– Hückel theory is known to break down in salt concentrations above ca. 5–10 mM (1–2 orders of magnitude below salt concentrations typically seen in coacervates) [77]. Indeed, it has been suggested that the apparent matching is a result of both the liberal use of a number of fitting parameters (χ, α, σ) as well as a cancellation of errors from both the connectivity-based correlations that enhance coacervation and the excluded volume repulsions that suppress coacervation [122].

Beyond the fundamental understanding of coacervates, the desire to probe increasingly complex systems, with multiple blocks [32,41,123], new chemical functionalities [56], and more advanced architectures [67,68,124], has inspired the development of new theoretical and computational tools for understanding coacervates and other charged complexes. A number of strategies have emerged to address the limitations of historical theoretical development, expanding the predictive power for designing this emerging class of materials. We group current, modern developments into a number of broad classes, each with its own set of advantages and disadvantages.

4.2. The complexation approach

RPA work by Borue and Erukhimovich specifically considered the case of a polyelectrolyte complex that forms a globular structure [98]. Their work postulated that these globular complexes can aggregate to form complex coacervates, due to a tradeoff between the increase in hydrated area versus benefits of the translational entropy of the counterions [98]. In the spirit of this hypothesized link between complexes and coacervates, a class of theories has focused on developing the theory of complexes and subsequently applying them to multi-chain coacervate systems [62,66,105,125].

Complexation theory spans a number of underlying approaches; Borue and Erukhimovich initially used RPA to capture the competition between correlated charge interactions and single-chain entropy [98]. In contrast, modern theoretical approaches adapted ideas based on classical Manning condensation theory in order to characterize systems that were understood to be outside the realm of RPA-based methods (i.e. high charge densities) [52,126]. Manning condensation arose from the electrostatic potential around a chain of charge density σ , which leads to diverges at a sufficiently high value of the linear charge density [126]. Manning's argument is based on the partition function of a line of charge in the presence of nearby charges of the opposite sign. The *nearest* free charge is affected by the unscreened Coulombic interaction with the line of charge, $\beta u(r) = 2\sigma \lambda_B \ln r$, which leads to the form of the partition function for monovalent ions [126]:

$$\mathcal{Z} = \mathcal{Z}_0 \int_0^{r_0} dr \, 2\pi r \exp(-\beta u(r)) = 2\pi \mathcal{Z}_0 \int_0^{r_0} dr \, r^{1-2\sigma\lambda_B} \tag{7}$$

The constant \mathcal{Z}_0 contribution stems from the non-nearest ions beyond a distance r_0 , which feel the screened environment and undergo the standard Debye–Hückel screening [126]. The integral associated with the nearest charge, however, diverges unless the exponent in the integrand is $1 - 2\sigma\lambda_B < -1$ [126]. The interpretation of this is that charges will avoid the divergence by 'condensing' on to the line of charge (i.e. the polyelectrolyte), so that it can realize an 'effective' linear charge density of $\sigma_{eff} = 1/\lambda_B$, or a single charge per Bjerrum length (Fig. 4a) [103,104,126].

Manning condensation has strong ramifications for complex formation. Almost all theories on complexation invoke some form of 'counterion release' theory [62,66,127]; in an uncomplexed chain the condensed counterions are confined to the chain, however these counterions can be replaced by the oppositely charged chain and gain translational entropy. This leads to the straightforward result for the entropy change as two chains form a complex, each with *N* monomers [66]:

$$\Delta S \approx -2Nk_B \alpha \ln \phi_S \tag{8}$$

Here, α is the fraction of condensed counterions and ϕ_s is the volume fraction of salt.

Condensed ions also play a significant role in non-stoichiometric complexes, and destabilize complex formation due to their localization in the globule. Work by Zhang and Shklovskii mapped out a phase diagram describing the behavior of complexes as their stoichiometry and relative lengths changed [127]. Motivated by bridging the gap between polymer/multivalent ion theories and complexation theories, a series of different 'morphologies' of these systems were predicted [127]. This includes globular complexes at stoichiometry, which then move through 'tadpole' regimes (Fig. 4b) to reach an uncomplexed state at high out-of-stoichiometric ratios [127,128].



Fig. 4. (a) Manning condensation theory is based on the observation that the calculation of the partition function Z can diverge when considering the *closest* charge next to a chain of the opposite charge. This divergence is physically avoided by *condensing* counterions onto the chain, lowering its charge density σ to one charge per Bjerrum length λ_B [126]. (b) Using counterion condensation ideas, Shklovskii and Zhang predicted the formation of globular and tadpole globules for soluble complexes [127], which are correspondingly seen in simulations [128]. Reprinted from Physica A, 352, Zhang R and Shklovskii Bl, Phase Diagram of Solution of Oppositely Charged Polyelectrolytes, 2005 with permission from Elsevier; and Dias, RS et al. reprinted with permission from Wiley. (c) The driving force for complexation is called *counterion release*. Ou and Muthukumar observe this in simulations, where counterions are localized next to two non-interacting polyelectrolytes (top) [66]. When these chains complex, counterions are no longer localized and gain translational entropy. Reprinted with permission from Ou Z and Muthukumar M J. Chem. Phys. 2006;124:154,902. Copyright 2006, AIP Publishing LLC. (d) Extension to non-equilibrium complexes has been suggested by Schlenoff et al., who use a 'doping' model where counterion release is quantified by the fraction of unmatched polycation–polyanion pairs *y* [51,135]. Reprinted with permission from non-equilibrium complexes to coacervates to fully miscible solutions [51,135].

Simulation is consistent with these results [66,128], demonstrating that 'counterion release' is the driving force for polyelectrolyte complex formation (Fig. 4c). DNA/polyelectrolyte complexes useful for drug delivery motivate work on complexes, and many of the simulation efforts have focused on incorporating relevant molecular details [56,59,62, 65–68,129–134]. This includes the structure (charge density and flexibility) of DNA molecules, as well as the nature of the complexing polymer as well [56,59,62,129–133]. Effects such as charge sequence and architecture have been shown to play an important role in the stability and morphology of complexes [56,62,129,131].

Efforts to extend these results to polyelectrolyte coacervates have been considered relatively infrequently. Despite the utility for complexation, there is not a clear way to proceed to macroscopic coacervate phases that lack the 'ordering' typically found in a complex. This 'disorder' is due to (1) the remaining presence of significant amounts of salt and counterion charges that still interact with the coacervating chains [55] and (2) the lack of one-to-one correspondence between chains (i.e. each chain is interacting with many others). Recently, attempts to consider this viewpoint by Schlenoff et al. have used a *doping* picture of complex coacervates that extends from a disordered polyelectrolyte complex into a more dilute, macroscopic polyelectrolyte pictures (Fig. 4d) [51,55,135]. This is tied to a 'complex/coacervate continuum' conceptual picture that has emerged from experimental observation [51]. The approach is to slowly dope or replace charges initially paired between complexed polyelectrolytes with ion pairs [135]. The polyelectrolytes get increasingly 'coacervate-like' as the amount of ion pairs that replace complexation gets above a threshold value [51, 135]. The critical salt concentration for coacervation is linked to complete removal of complexed ion pairs [51,135]. It remains unclear that this approach will hold for many cases, or if it will provide conceptual guidance or prediction. Indeed, this 'ion pair' picture is reminiscent of historic work using the concept of ion clustering to explain correlations in regular electrolyte solutions at low temperatures [136]. While they can qualitatively agree with certain experimental features, such approaches are ad hoc and typically neglect higher-order correlations present in charged systems and limit predictive power [137,138]. This theoretical approach remains a challenge regardless, due to the importance of the Hofmeister series in a number of coacervate systems [55,81,115], which may be exacerbated by the use of highly charge-dense polymers (such as poly(styrene sulfonate) and poly(diallyldimethylammonium)) used in many of these studies [51, 55, 57, 115, 135].

4.3. The field theory approach

Voorn-Overbeek and RPA approaches stem from the same theoretical origins, with the RPA being the Gaussian field correction to the mean-field theories on which Voorn-Overbeek is based [16,52-54,75, 98]. Parallel to similar developments in the behavior of other polymeric materials such as block copolymers [84,92], efforts have been made to use numerical field theoretic methods to treat the inadequacies of analytical approaches to understand complex coacervates [41,139–143]. Block copolymers have benefited from years of research into self consistent field theory (SCFT), which is capable of capturing the mean-field behavior of common inhomogeneous systems [84]. The main concept behind SCFT and related field theoretic approaches is to solve the partition function in the form of Eq. (3) using a Hamiltonian such as the one in Eq. (4) for charged systems. Instead of integrating out the non- ϕ fields, and also without invoking the mean-field approximation, it is possible to transform the integral into one that depends only on the fields μ and ψ [84,144]. For complex coacervates, the resulting partition function becomes [139,141,142]:

$$\mathcal{Z} \sim \int \mathcal{D}\mu \int \mathcal{D}\psi \exp(-\beta \mathcal{H}_{\text{Coac}}[\mu, \psi]) \tag{9}$$

When dispersive χ -interactions are neglected and replaced with simple excluded volume repulsions parameterized by u_0 , the updated Hamiltonian is [139,141,142]:

$$\beta \mathcal{H}_{\text{Coac}} = \frac{1}{2} \int d\mathbf{r} \left[\frac{|\nabla \psi|^2}{4 \pi \lambda_B} - \frac{\mu^2}{u_0} \right] - n_{P+} \ln Q_{P+} [-\mu + \psi] - n_{P-} \ln Q_{P-} [-\mu - \psi] - n_{C+} \ln Q_{C+} [\psi] - n_{C-} \ln Q_{C-} [-\psi]$$
(10)

A number of pedagogical texts and articles demonstrate the practical implementation of an iterative scheme to numerically calculate the results of this theory [84,144]. Numerical calculations require the calculation of the single-chain partition function given by $VQ_{P\pm}[-\mu \pm \psi] = \int d\mathbf{r}q_{\pm}(\mathbf{r}, s = 1; [-\mu \pm \psi])$, where the s = 1 indicates that this is the sum over the weight of all chain ends at \mathbf{r} after traversing the field $-\mu \pm \psi$ [84,144]. The rest of the chain had been propagated through this field using the diffusion equation $\frac{\partial q_{\pm}}{\partial s} = \nabla^2 q_{\pm} - (-\mu \pm \psi) q_{\pm}$ integrated from s = 0 [84,144]. The single-particle partition functions $VQ_{C\pm}[\pm\psi] = \int d\mathbf{r} \exp[\mp\psi]$ are similarly calculated [84,144]. SCFT involves an iterative scheme involving this calculation of the Hamiltonian, as well as its field derivatives $(\frac{\partial H_{cont}}{\partial \mu})_r$ at each point \mathbf{r} to update the fields to reach an extremum in the Hamiltonian [84,144]:

$$\left(\frac{\partial \mathcal{H}_{Coac}}{\partial \mu(\mathbf{r})}\right)_{\boldsymbol{\mu}^*} = 0; \left(\frac{\partial \mathcal{H}_{Coac}}{\partial \psi(\mathbf{r})}\right)_{\boldsymbol{\psi}^*} = 0$$
(11)

Here, the asterisks denote the *mean-field* value of the Hamiltonian, determined iteratively as these derivatives themselves depend on the value of the fields that have been extremized.

In a homogeneous system, this method is essentially equivalent to the mean-field picture discussed in Eq. (4) (except for the neglect of the dispersive terms). The single-polyelectrolyte version of this theory has been dubbed the 'Model F' field theory [84,88], and has been applied to a number of situations for polyelectrolyte block copolymers [145, 146]. This theory is now considered inadequate for many polymer systems including block copolyelectrolytes [12,147] as well as complex coacervates [12], stemming from a variation of the same observation made about the homogeneous mean-field theory: the electrostatic term of the Hamiltonian is only non-zero when there is charge separation between the grid points in the numerical solution to Model F [148]. Therefore, the only difference in energy between a macroscopic phase without charges and a charged, electrostatically neutral phase is if there are more components in the latter (such as salt or counterions) that possess additional translational entropy. This is noticeably unphysical for polymer systems such as complex coacervates, where favorable electrostatic interactions within an otherwise homogeneous phase must be accounted for.

Extending field theory to capture coacervate behaviors requires sophisticated techniques beyond the mean-field approximation used in SCFT [84,92,144]. This is analogous to the development of RPA, which needed the first-loop expansion of the inverse scattering function to couple connectivity and electrostatic attraction [52-54]. In numerical field theories, moving beyond the mean-field approximation means considering the influence of more than one set of fields into the partition function sum. The inclusion of more than one set of fields rather than just the mean-field means that these incorporate all 'field fluctuations' (the far right schematic in Fig. 3a) [144,149]. These fluctuations are included using a variety of methods, such as 'complex Langevin' methods that use a pseudo-dynamic field update or a Monte Carlo approach where changes to the field are randomly done and subsequently evaluated via the system Hamiltonian [84,144]. Recently, these non-meanfield methods have been developed to treat a broad class of polymer science problems, such as semidilute solutions [150], block copolymers [151], and nanoparticle/block copolymer composites [152].

Complex coacervates have been among the polymer systems studied using non-mean-field methods, which have been used to develop predictions for a number of experimental investigations. Popov, Lee, and Fredrickson developed a complex Langevin technique to model coacervates [141,142] demonstrating that its predictions are largely consistent with the results of one-loop RPA, except in high charge densities (Fig. 5a) [141,142]. Improvements on this model consider the use of a 'smearing function' that provides a finite size for the charges in the field theory, which ensures that the model is 'UV convergent' if the finite size of the grid used in the numerical calculation is sufficiently small to capture all charge details [139]. In principle, this approach is capable of providing a full theoretical picture of complex coacervates, as it completely evaluates the partition function given in Eqs. (3) and (4). However, the grid that is used is on a similar size as the size of the individual ions [139]. While this still allows the thermodynamics of a homogeneous coacervate system to be captured, there remain challenges in scaling up the calculation to consider inhomogeneous systems that are of experimental interest (and can be 2-3 orders of magnitude larger).

Recent efforts to extend fluctuating field theories to larger length scales have been motivated by the desire to consider block copolymer-based coacervates. In particular, Audus et al. have developed an 'embedded fluctuation' model that incorporates the one-loop RPA model directly into an SCFT calculation [32,41], capitalizing on the observation that the complex Langevin and analytical one-loop RPA models are mostly in agreement (Fig. 5a). This model is capable of exhibiting impressive agreement with experimental phase diagrams (Fig. 5b) [41].

These sophisticated field theoretic approaches are powerful techniques that can treat inhomogeneous polyelectrolyte coacervates; as these materials become increasingly complicated, field theories represent a promising way to develop their theoretical understanding. Nevertheless, these methods possess similar drawbacks to their RPA forebears. While the full fluctuating field theory is capable of considering more highly-charge dense systems [139], it has so far not been used in larger scale calculations for block copolymers. The one-loop RPA result is used instead, however it is limited when polymers have a high charge density along their backbone [41]. Therefore, real coacervate-based self-assembled systems may remain poorly described by even these sophisticated methods. Furthermore, the use of Gaussian smearing functions even in the fluctuating techniques may limit their ability to articulate the local charge structure; while chain length-scale scattering functions is resolved, as far as we know the ion and charge correlation functions in complex coacervates have not been demonstrated using these methods [139].



Fig. 5. (a) The charge–charge scattering function *S*_{CC}(*k*) calculated via the full field theoretical approach (points) is able to demonstrate good matching to RPA-based analytical theory (lines) [142]. This is especially true for small values of charge density (parameterized by *E*), however significant deviations at high *E* occur at large values of *k* [142]. This is consistent with known limitations of RPA [52]. Reprinted with permission from Riggleman, RA, et al. Chem. Phys. 2012;136:024,903. Copyright 2012, AIP Publishing LLC. (b) The accuracy of RPA-based analytical theory has led to the development of the 'embedded fluctuation' model that incorporates the one-loop RPA results into SCFT [41]. Experimental results (main graph) match theoretical predictions (inset) [41]. Reproduced in part from [40] with permission of The Royal Society of Chemistry.

4.4. The simulation approach

Field theory and counterion release theory have provided conceptual guidance for coacervation and complexation respectively. While they remain incredibly useful, they reflect only a highly idealized picture of real polyelectrolyte complexes. This stems from some very important assumptions that are made. For example, these theories almost exclusively use some version of the restricted primitive model that considers all species to be composed of charged spheres in a dielectric medium (Fig. 6a) [78]. There are a lot of approximations wrapped up in this statement: atomistic detail is neglected including the behavior of the solvent (typically water), ions have a specific size that includes a hydration shell, and the dielectric constant is homogenous. Each of these approximations has been appropriately called into question, and can be demonstrated to play a role in a number of situations [51,56,71,109, 110,112,134,135,153]. Furthermore, almost all of the previous theoretical methods include assumptions of thermodynamic equilibrium, despite the observation that many complex or coacervate systems are strongly trapped in metastable or non-equilibrium states [51,56,71, 116,153]. Finally, other molecular interactions are typically neglected yet may play a crucial role [56,134].

Atomistic structure, kinetic trapping, and secondary interactions are all behaviors that require atomistic or molecular simulations. Simulations have begun to probe these challenging effects. For example, the formation of glassy-like dynamics in layer-by-layer assembly has been studied by considering local dynamics in molecular dynamics (MD) simulations [153]. These studies have implicated hydrogen bonding and complexation as cooperative affects that strongly slow down the dynamics of charge polymer systems (Fig. 6b). Similarly, the role of hydrogen bonding and chirality (Fig. 6c) in the formation of kinetically trapped precipitates rather than coacervates has highlighted the importance of atomistic structure on the behavior of charge polymer systems [56,134].

However, atomistic simulation of complexation is still an open field for a number of reasons. Most importantly, the length and time scales that MD is able to capture limit their applicability to homogeneous



Fig. 6. (a) The restricted primitive model provides the starting point for almost every theoretical approach to studying electrostatics, because it coarse-grains atomistic features as charged beads [12]. The neglect of these atomistic details represents a primary limitation of most theories, which can only (partially) be overcome by using atomistic simulation. (b) Molecular dynamics simulations demonstrate the importance of hydrogen bonding in dense coacervate systems [153]. The diffusion of water is shown to undergo a discrete jump in its diffusion coefficient, related to the formation of a 'network' of hydrogen bonding [153]. Reprinted with permission from Yildirim et al. ACS Macro Lett. 2015;4:1017–1021. Copyright 2015 American Chemical Society. (c) Chirality also plays a significant role, with out-of-equilibrium complexes formed in stereoregular polypeptides and coacervates formed in otherwise-equivalent racemic polypeptides [56,134]. Typical snapshots from simulation demonstrate that strong interactions are consistently more common when both chains are chiral [56,134]. Reproduced in part from [133] with permission of The Royal Society of Chemistry.

systems and very short time scales. Many of the issues associated with polyelectrolyte complexes span hundreds of nanometers or microseconds to minutes of time; these are orders of magnitude outside the range of atomistic MD simulation. The atomistic challenges in polyelectrolyte complexes themselves also represent a number of very active fields and lingering challenges in MD simulations: the structure and dynamics of water [154], the size and behavior of ions (via the Hofmeister series) [120], and the nature of hydrogen bonding [155] are all nontrivial and prevent atomistic simulation from providing unwavering predictive power.

5. A unified theory of complex coacervation?

Modern coacervate and complexation theory has made great strides in providing a comprehensive picture of charged polymers. A broad palette of theoretical and computational methods informs materials development, however by and large the models that have been created to date lack a fully predictive capability of all complex coacervates. Some limits (low charge density, homogeneous systems) are well characterized by field theoretical models [16,18,41,52,75,139,140,142], while other limits (high charge density, homogeneous or single-complex systems) can be well-described by counterion release ideas [57,59,62, 66,68,118]. Nevertheless, systems that are inhomogeneous (i.e. block copolymers, blends, brushes), kinetically trapped, and have significant atomistic-level structure or charge patterns are still in need of further theoretical development. A unified theory of complex coacervation is still missing.

Hints of how this theory might be developed are starting to emerge. One area of convergence would be to bridge the gap between field theoretical methods and counterion release methods. One candidate theory uses a liquid state theory model known as the Polymer Reference Interaction Site Model (PRISM) [156,157] to develop an alternative theory of complex coacervation [122]. It is shown that this theory is capable of demonstrating both counterion release (Fig. 7a,b) and, in the appropriate limit, approaches the Voorn-Overbeek theory (Fig. 7c) [122]. PRISM and related liquid state theory models are capable of capturing correlation effects of (for example) hard spheres and structured molecules, and subsequently providing macroscopic thermodynamic parameters that can be used to calculate phase behaviors [156,157]. This theoretical approach captures aspects difficult or impossible to calculate in RPA, field theoretic approaches, or counterion release. Importantly, PRISM predicts pair correlation functions that capture local charge structure typically included in an ad hoc fashion using ion pairing arguments [52,66,141].

However, this theory falls short of a true unified theory due to deficiencies in the underlying PRISM model. These theories require what are known as 'closure approximations' that are often unreliable with regards to macroscopic thermodynamic values [78]. The closure used in this particular example (the Debye–Hückel Extended Mean Spherical approximation) [158] is also not optimized for use with the PRISM formalism. PRISM is further limited to describing equilibrium states in homogeneous systems, however there are methods capable of circumventing these limitations for incorporating PRISM into larger scale theories [159,160]. Despite these quantitative challenges, this is the first example of a theory capable of reflecting both counterion release and Voorn–Overbeek limits [12,122]. It has also highlighted the importance of charge density and the excluded volume of charges in the continued development of theory [12,122].

The embedded fluctuation model of Audus et al. also provides the starting point for increasingly accurate theoretical or computational approaches to complex coacervates [41]. By coupling RPA results to field theoretical calculations, multiple length scales of molecular information are incorporated into a single model. This is part of an emerging class of multi-scale models that are beginning to address the wide variety of length scales at play in a single-polyelectrolyte system [41,90,147,148, 161–163]. Similar models combining liquid state theory and SCFT are capable of capturing melt polymer systems [90,147,148,161-163], for example, as are field theory models that incorporate molecular conformation information for polymer brushes and gels [164,165]. A more complete theory of complex coacervate may take a similar approach. By leveraging molecular simulation or alternative field theoretic methods [166,167], multi-scale models of complex coacervation may be able to guide conceptually or even predict material properties for charged selfassembly. Molecule-specific behavior, such as atomistic structure, water, and hydrogen bonding may even be possible in such an approach.

In Fig. 8 we map out the various theoretical models that have been discussed in this review. Two general features demarcate the essential aspects captured or neglected in each model: the length scale that they consider, and the linear charge density σ . Low σ is characterized by a lack of counterion condensation, with charges separated by more than a λ_B of distance. High σ includes models that can account for counterion condensation, either explicitly (such as with molecular dynamics) or using counterion release arguments. Field theoretic arguments can, in principle, also account for this, however the 'smearing' of charges places an upper limit on its accuracy. Voorn-Overbeek, RPA, and the embedded fluctuation theory are limited to low- σ regimes. Coacervate theories resolve different length scales L. For example, all RPM-based theories (Voorn-Overbeek, counterion release, PRISM, etc.) are not capable of resolving atomistic details below ~1 nm, an area that MD simulations are able to capture. Conversely, MD is not able to efficiently calculate systems above ~10-100 nm, limiting its use in representing the overall phase behavior of coacervation and larger length scales. Large length scales - those associated with self-assembly > 10-100 nm, have been described primarily by the embedded fluctuation model.



Fig. 7. PRISM model of complex coacervation captures both counterion release as well as the Voorn–Overbeek limit. (a) Pair correlations calculated in the dense coacervate phase, which demonstrate strong polyanion/polycation (P+, P–) attractions [122]. In this phase, the opposite polymer/charge correlations are almost indistinguishable from the charge/charge correlations (blue curve and red curve, respectively) [122]. (b) The same calculation in the dilute phase demonstrates that there is an excess of salt near the oppositely charged polymer when compared to oppositely charged salt ions [122]. This reflects counterion condensations that are 'released' when the polymers move into the dense phase. (c) In the limit of low linear charge densities along the polyelectrolyte chains σ , as well as at low concentrations and small ion sizes, thermodynamic values from PRISM such as the excess chemical potential μ_{\pm} approach the Debye–Hückel prediction (black line) [122]. Reprinted with permission from Perry SL and Sing CE, Macromolecules. 2015;48:5040–5053. Copyright 2015 American Chemical Society.



Fig. 8. Map of the various theories discussed in this review. The realm of applicability of these theories is considered as a function of both the length scale that it can resolve, *L*, and the linear charge density of the polymers σ . Important length scales are the atomistic (~1 Å) length scale, the coarse-grained length scale captured by the restricted primitive model (RPM, ~1 nm), and the self-assembly length scale ($\geq 10 - 100$ nm). Noting that σ determines the relevant length scales, we draw a non-rigorous 'empty area' in the lower left hand side of the diagram. Models included are Voorn–Overbeek and RPA (VO, RPA), field theoretic (FT), counterion release (CR), molecular dynamics simulation (MD), polymer reference interaction site model (PRISM), and the embedded fluctuation model (EF). We note that, even within their realms of applicability, these methods all possess different levels of accuracy.

Not all *L* values are relevant for all σ . For example, with low σ systems the density of the coacervate tends to be very small, and large length-scale features (chain correlations) drive coacervation rather than small length-scale features (such as atomistic structure). We denote this general observation by shading the small *L*, small σ region of Fig. 8. This is not a rigorous boundary, however, especially when other

interactions (dispersive, hydrogen bonding, metal-ligand, etc.) begin to play a central role.

Fig. 8 highlights what is currently missing in coacervate theory. First, an accurate description of large length scales for high charge density polyelectrolytes is missing. This is the upper right hand corner of the diagram, and is where much of the emerging coacervate-based assembled

Table 1

1000						
- H 1	be current models of poly	mor complay concomistion	discussed in this paper	up cluidup a the advantage	lumpitations and	productions of each model
	<u>NA CHEPANE INVALAIS AL NAIVE</u>	<u></u>	merneepri in thie hange		num anne ann	INPANANCIANC ALPSAN INAAP
					111111111111111111111111111111111111111	
_				,		p

Method	Advantages	Limitations	Predictions	Key References
Voorn–Overbeek	 Simple analytical form Good matching to experimental phase diagrams 	 Matching to experimental phase diagrams requires fitting constants, cancellation of errors Neglects charge connectivity along chain Neglects finite size of ions, polymer charges Equilibrium only Mean-field 	 Coacervation phase diagram Thermodynamic values such as surface tension, free energies, salt partitioning 	[16,18,28,75,79,81,82]
RPA	 Analytical equations Can be modified to include ion charge, local correlations Can be systematically extended to include higher-order correlations Slightly beyond mean-field 	 Inclusion of connectivity, charge size ad hoc Systematic inclusion of higher-order charge correlations becomes challenging; highly charge-dense polymers not adequately described Equilibrium only 	 Coacervation phase diagram Thermodynamic values such as surface tension, free energies, salt partitioning Chain scattering functions 	[52–54,73,98]
Field Theoretic	 Can calculate charged systems without any major assumptions Beyond mean-field 	 Requires small grid to resolve all charge organization features Small grid limits ability to compute large-scale heterogeneous polymer systems Equilibrium only 	 Coacervation phase diagram Thermodynamic values such as surface tension, free energies, salt partitioning Local correlations, scattering functions 	[139–142]
Counterion release	 Conceptually simple Captures entropic driving force for coacervation Captures high charge density limit 	 Not yet developed into full theory for coacervation Requires counterion condensation (high charge density) limit Does not describe small enthalpic contributions to coacervation Equilibrium only 	 Entropic contribution of coacervation Critical salt concentration 	[51,62,66–68,128,135]
Molecular dynamics	 Atomistic resolution Dynamic information (non-equilibrium) 	Small length, time scalesRelies on the accuracy of force fields	 Local dynamics Solvent, local chain and charge structure 	[56,59-61,65,134,153]
Embedded fluctuation	 Can capture coacervate-driven block copolymer self-assembly Slightly beyond mean-field (RPA) 	 Uses 1-loop RPA for local charge correlations (same limitations) Polymers treated at mean-field level (SCFT) Equilibrium only 	 Coacervate-driven block copolymer morphology phase diagrams Chain scattering functions 	[41]
PRISM	 Can describe both Voorn Overbeek, counterion release limits (all charge densities) Captures both local charge organization and phase behavior Beyond mean-field 	 Opaque assumptions that are difficult to systematically improve Thermodynamic values from PRISM are highly dependent on closure, and often not quantitative Equilibrium only 	 Coacervation phase diagram Local correlations 	[122]

materials lie. This regime remains an important area to understand. Second, there are few methods that span all length scales. The ability to include atomistic, nanometer, and self-assembly length scales remains a challenge. This is more important at high σ , where all of these length scales matter. Third, the existing patchwork of theories all still have advantages and disadvantages that are not easily captured by this diagram. For example, PRISM can reach all chain densities, yet still requires significant refinement to do so accurately [78,122]. Voorn-Overbeek fails to demonstrate the entropic driving force for coacervation [16,118], despite providing excellent matching to experiment [18]. Finally, almost all of these theories are essentially equilibrium theories; except for MD [63,153], the dynamics of coacervates have not been widely studied using theory or simulation. We summarize the advantages and disadvantages of using all of these methods in Table 1, which also describes the main predictions of each theory or simulation that can be compared to experiment.

6. Conclusion

Polyelectrolyte coacervates and complexes are a class of materials that are being increasingly used for self-assembly [31–33,35,41], however there are fundamental challenges in understanding them from a theoretical point of view. Many if not most of the most pressing challenges in polymer modeling today affect have profound implications for complex coacervates – highly correlated electrostatics [12,94, 147,161,162], multiple length scales, kinetic traps and glassy dynamics [41,51,55,153], water [153], dielectric [97], and specific ion effects [45, 81,115].

The diversity of modern theoretical approaches typically address some but not all of these issues. A comprehensive picture of the state of the theory shows that while a patchwork of many theories collectively captures a number of limiting cases, there is not a single theory capable of simultaneously addressing the full spectrum of features observed in complex coacervation. Ideally, such a theory would be able to predict coacervate properties over a broad range of parameters and length scales. At the atomistic and/or molecular level, the organization of charges and even solvent would be characterized by (for example) pair correlation functions. Larger length-scale effects, such as the overall polymer conformation, phase behavior, and self-assembled structures, would be simultaneously predicted. Out-of-equilibrium behavior should also be captured in a complete physical picture of coacervation. Finally, such a theory would ideally provide a consistent conceptual picture of coacervation that is useful for experimental design of coacervatebased materials.

Intermediate progress toward this goal would lead to immediate impact. For example, to the author's knowledge the rheological behavior of coacervates has not been widely studied from a theoretical perspective. This is despite the regular use of rheology as a tool to characterize coacervates [35,80]; existing models such as transient network theory or sticky reptation may be useful in understanding rheological observations [168–170]. Drawing such a connection between rheology and molecular structure would increase the information obtained from these investigations. Likewise, self-assembly in high charge density polymers leverages the entire hierarchy of length scales in charged materials. Fully atomistic control over self-assembled structures is in principle possible, however theoretical prediction is needed to realize this limit.

There is still a need for more connection between experimental and theoretical work. Experimental efforts have largely focused on phase behavior as the primary point of comparison, however this is not always a direct probe of the molecular-level features such as charge correlations, charge density effects, excluded volume, and specific ion effects. This makes it difficult to distinguish between Voorn–Overbeek theory and more sophisticated theories, which as a result are not often compared to experiment. Conversely, there is a need from the theoretical side to expand the palette of models relevant to the coacervate-driven assembly that is at the forefront of experimental work in the field. Joint efforts will expedite the convergence on an overall picture of coacervation; this will hopefully enable polymer scientists to fully exploit their complexity to make truly exciting and biologically inspired materials.

Acknowledgments

C.E.S. thanks Mithun Radhakrishna for proofreading manuscript.

References

- [1] Fuoss RM. Polyelectrolytes. Discuss Faraday Soc 1951;11:125–34.
- [2] Flory PJ. Principles of polymer chemistry. Ithaca: Cornell University Press; 1953.
- [3] Dobrynin AV, Rubinstein M. Theory of polyelectrolytes in solutions and at surfaces. Prog Polym Sci 2005;30:1049–118. <u>http://dx.doi.org/10.1016/j.progpolymsci.2005</u>. 07.006.
- [4] Netz RR, Andelman D. Neutral and charged polymers at interfaces. Phys Rep 2003; 380:1–95. http://dx.doi.org/10.1016/S0370-1573(03)00118-2.
- [5] Young WS, Kuan WF, Epps TH. Block copolymer electrolytes for rechargeable lithium batteries. J Polym Sci B 2014;52:1–16. <u>http://dx.doi.org/10.1002/polb.23404</u>.
- [6] Hallinan DA, Balsara NP. Polymer electrolytes. Annu Rev Mater Res 2013;43: 503–25. http://dx.doi.org/10.1146/annurev.ms.16.080186.001333.
- [7] Fogolari F, Brigo A, Molinari H. The Poisson-Boltzmann equation for biomolecular electrostatics: a tool for structural biology. J Mol Recognit 2002;15:377–92. http://dx.doi.org/10.1002/jmr.577.
- [8] Turgeon SL, Schmitt C, Sanchez C. Protein–polysaccharide complexes and coacervates. Curr Opin Colloid Interface Sci 2007;12:166–78. <u>http://dx.doi.org/10.1016/</u> j.cocis.2007.07.007.
- Kayitmazer A, Seeman D, Minsky B, Dubin P, Xu Y. Protein–polyelectrolyte interactions. Soft Matter 2013;11:2553–83. http://dx.doi.org/10.1039/c2sm27002a.
- [10] Stewart RJ, Wang CS, Shao H. Complex coacervates as a foundation for synthetic underwater adhesives. Adv Colloid Interface Sci 2011;167:85–93. <u>http://dx.doi.</u> org/10.1016/j.cis.2010.10.009.
- [11] Israelachvili JN. Intermolecular and surface forces. 3rd ed. Waltham, MA: Academic Press; 2011.
- [12] Radhakrishna M, Sing CE. Charge correlations for precise, Coulombically driven self assembly. Macromol Chem Phys 2016;217:126–36. <u>http://dx.doi.org/10.1002/</u> macp.201500278.
- [13] Bungenberg de Jong HB, Kruyt HR. Coacervation (partial miscibility in colloid systems). Proc K Ned Akad Wet 1929;32:849–56.
- [14] de Kruif CG, Weinbreck F, de Vries R. Complex coacervation of proteins and anionic polysaccharides. Curr Opin Colloid Interface Sci 2004;9:340–9. <u>http://dx.doi.org/10. 1016/j.cocis.2004.09.006.</u>
- [15] Cooper CL, Dubin PL, Kayitmazer AB, Turksen S. Polyelectrolyte–protein complexes. Curr Opin Colloid Interface Sci 2005;10:52–78. <u>http://dx.doi.org/10.1016/j.cocis.</u> 2005.05.007.
- [16] Overbeek JT, Voorn MJ. Phase separation in polyelectrolyte solutions; theory of complex coacervation. J Cell Physiol Suppl 1957;49:7–22. <u>http://dx.doi.org/10.</u> 1002/jcp.1030490404 [discussion, 22–6].
- [17] Voets IK, de Keizer A, Cohen Stuart MA. Complex coacervate core micelles. Adv Colloid Interface Sci 2009;147-148:300–18. <u>http://dx.doi.org/10.1016/j.cis.2008.</u> 09.012.
- [18] Spruijt E, Westphal AH, Borst JW, Cohen Stuart MA, van der Gucht J. Binodal compositions of polyelectrolyte complexes. Macromolecules 2010;43:6476–84. <u>http://</u> dx.doi.org/10.1021/ma101031t.
- [19] de Vries R, Cohen Stuart M. Theory and simulations of macroion complexation. Curr Opin Colloid Interface Sci 2006;11:295–301. <u>http://dx.doi.org/10.1016/j.</u> cocis.2006.09.004.
- [20] van der Gucht J. Spruijt E, Lemmers M, Cohen Stuart MA. Polyelectrolyte complexes: bulk phases and colloidal systems. J Colloid Interface Sci 2011;361: 407–22. http://dx.doi.org/10.1016/j.jcis.2011.05.080.
- [21] Wang Y, Kimura K, Dubin PL, Jaeger W. Polyelectrolyte-micelle coacervation: effects of micelle surface charge density, polymer molecular weight, and polymer/surfactant ratio. Macromolecules 2000;33:3324–31. <u>http://dx.doi.org/10. 1021/ma991886y.</u>
- [22] Schmitt C, Turgeon SL. Protein/polysaccharide complexes and coacervates in food systems. Adv Colloid Interface Sci 2011;167:63–70. <u>http://dx.doi.org/10.1016/j.cis.</u> 2010.10.001.
- [23] Tolstoguzov VB. Some physico-chemical aspects of protein processing into foodstuffs. Food Hydrocoll 1988;2:339–70. <u>http://dx.doi.org/10.1016/S0268-005X(88)80001-8.</u>
- [24] Yeo Y, Bellas E, Firestone W, Langer R, Kohane DS. Complex coacervates for thermally sensitive controlled release of flavor compounds. J Agric Food Chem 2005; 53:7518–25. http://dx.doi.org/10.1021/jf0507947.
- [25] Matalanis A, Jones OG, McClements DJ. Structured biopolymer-based delivery systems for encapsulation, protection, and release of lipophilic compounds. Food Hydrocoll 2011;25:1865–80. http://dx.doi.org/10.1016/j.foodhyd.2011.04.014.
- [26] Jourdain L, Leser ME, Schmitt C, Michel M, Dickinson E. Stability of emulsions containing sodium caseinate and dextran sulfate: relationship to complexation in solution. Food Hydrocoll 2008;22:647–59. <u>http://dx.doi.org/10.1016/j.foodhyd.2007</u>. 01.007.

- [27] Weinbreck F, de Vries R, Schrooyen P, de Kruif CG. Complex coacervation of whey proteins and gum Arabic. Biomacromolecules 2003;4:293–303. <u>http://dx.doi.org/</u> 10.1021/bm025667n.
- [28] Veis A, Aranyi C. Phase separation in polyelectrolyte systems. I. Complex coacervates of gelatin. J Phys Chem 1960;64:1203–10. <u>http://dx.doi.org/10.1021/</u> j100838a022.
- [29] Anema SC, (Kees) de Kruif CG. Co-acervates of lactoferrin and caseins. Soft Matter 2012;8:4471. http://dx.doi.org/10.1039/c2sm00015f.
- [30] Du X, Dubin PL Hoagland DA, Sun L. Protein-selective coacervation with hyaluronic acid. Biomacromolecules 2014;15:726–34. http://dx.doi.org/10.1021/bm500041a.
- [31] Fan Y, Tang S, Thomas EL, Olsen BD. Responsive block copolymer photonics triggered by protein-polyelectrolyte coacervation. ACS Nano 2014;8:11467–73. http://dx.doi.org/10.1021/nn504565r.
- [32] Krogstad DV, Choi S-H, Lynd NA, Audus DJ, Perry SL, Gopez JD, et al. Small angle neutron scattering study of complex coacervate micelles and hydrogels formed from ionic diblock and triblock copolymers. J Phys Chem B 2014;118:13011–8. http://dx.doi.org/10.1021/jp509175a.
- [33] Ortony JH, Choi S-H, Spruell JM, Hunt JN, Lynd NA, Krogstad DV, et al. Fluidity and water in nanoscale domains define coacervate hydrogels. Chem Sci 2013;5:58–67. http://dx.doi.org/10.1039/C3SC52368C.
- [34] Van Der Kooij HM, Spruijt E, Voets IK, Fokkink R, Cohen Stuart Ma, Van Der Gucht J. On the stability and morphology of complex coacervate core micelles: from spherical to wormlike micelles. Langmuir 2012;28:14180–91. <u>http://dx.doi.org/10.1021/</u> la303211b.
- [35] Korgstad DV, Lynd NA, Choi S-H, Spruell JM, Hawker CJ, Kramer EJ, et al. Effects of polymer and salt concentration on the structure and properties of triblock copolymer coacervate hydrogels. Macromolecules 2013;46:1512–8.
- [36] Hunt JN, Feldman KE, Lynd NA, Deek J, Campos LM, Spruell JM, et al. Tunable, high modulus hydrogels driven by ionic coacervation. Adv Mater 2011;23:2327–31. http://dx.doi.org/10.1002/adma.201004230.
- [37] Wang Y, Kimura K, Huang Q, Dubin PL, Jaeger W. Effects of salt on polyelectrolyte – micelle coacervation. Macromolecules 1999;32:7128–34. <u>http://</u> dx.doi.org/10.1021/ma990972v.
- [38] Harada A, Kataoka K. Chain length recognition: core-shell supramolecular assembly from oppositely charged block copolymers. Science 1999;283:65–7. <u>http://dx.doi.</u> org/10.1126/science.283.5398.65.
- [39] Cohen Stuart MA, Besseling NAM, Fokkink RG. Formation of micelles with complex coacervate cores. Langmuir 1998;14:6846–9. http://dx.doi.org/10.1021/la980778m.
- [40] Harada A, Kataoka K. Formation of polyion complex micelles in an aqueous milieu from a pair of oppositely-charged block copolymers with poly(ethylene glycol) segments. Macromolecules 1995;28:5294–9. <u>http://dx.doi.org/10.1021/</u> ma00119a019.
- [41] Audus DJ, Gopez JD, Krogstad DV, Lynd NA, Kramer EJ, Hawker CJ, et al. Phase behavior of electrostatically complexed polyelectrolyte gels using an embedded fluctuation model. Soft Matter 2015;11:1214–25. http://dx.doi.org/10.1039/C4SM02299H.
- [42] Pergushov DV, Müller AHE, Schacher FH. Micellar Interpolyelectrolyte complexes. Chem Soc Rev 2012;41:6888. http://dx.doi.org/10.1039/c2cs35135h.
- [43] Hwang DS, Zeng H, Srivastava A, Krogstad DV, Tirrell M, Israelachvili JN, et al. Viscosity and interfacial properties in a mussel-inspired adhesive coacervate. Soft Matter 2010;6:3232. http://dx.doi.org/10.1039/c002632h.
- [44] Priftis D, Farina R, Tirrell M. Interfacial energy of polypeptide complex coacervates measured via capillary adhesion. Langmuir 2012;28:8721–9. <u>http://dx.doi.org/10.</u> 1021/la300769d.
- [45] Lim S, Moon D, Kim HJ, Seo JH, Kang IS, Cha HJ. Interfacial tension of complex coacervated mussel adhesive protein according to the hofmeister series. Langmuir 2014;30:1108–15. http://dx.doi.org/10.1021/la403680z.
- [46] Feldstein MM, Dormidontova EE, Khokhlov AR. Pressure sensitive adhesives based on interpolymer complexes. Prog Polym Sci 2015;42:79–153. <u>http://dx.doi.org/10.</u> 1016/j.progpolymsci.2014.10.006.
- [47] Brangwynne CP. Phase transitions and size scaling of membrane-less organelles. J Cell Biol 2013;203:875–81. http://dx.doi.org/10.1083/jcb.201308087.
- [48] Keating CD. Aqueous phase separation as a possible route to compartmentalization of biological molecules. Acc Chem Res 2012;45:2114–24. <u>http://dx.doi.org/10. 1021/ar200294y</u>.
- [49] Koga S, Williams DS, Perriman AW, Mann S. Peptide–nucleotide microdroplets as a step towards a membrane-free protocell model. Nat Chem 2011;3:720–4. <u>http://</u> dx.doi.org/10.1038/nchem.1110.
- [50] Aumiller WM, Keating CD. Phosphorylation-mediated RNA/peptide complex coacervation as a model for intracellular liquid organelles. Nat Chem 2015;8. <u>http://dx.</u> doi.org/10.1038/nchem.2414.
- [51] Wang Q, Schlenoff JB. The polyelectrolyte complex/coacervate continuum. Macromolecules 2014;47:3108–16. <u>http://dx.doi.org/10.1021/ma500500q</u>.
- [52] Castelnovo M, Joanny JF. Complexation between oppositely charged polyelectrolytes: beyond the Random Phase Approximation. Eur Phys J E 2001;6:377–86. http://dx.doi.org/10.1007/s10189-001-8051-7.
- [53] Kudlay A, Olvera de la Cruz M. Precipitation of oppositely charged polyelectrolytes in salt solutions. J Chem Phys 2004;120:404–12. <u>http://dx.doi.org/10.1063/1.</u> 1629271.
- [54] Kudlay A, Ermoshkin AV, de la Cruz MO. Complexation of oppositely charged polyelectrolytes: effect of ion pair formation. Macromolecules 2004;37:9231–41. http://dx.doi.org/10.1021/ma048519t.
- [55] Schaaf P, Schlenoff JB. Saloplastics: processing compact polyelectrolyte complexes. Adv Mater 2015. http://dx.doi.org/10.1002/adma.201500176 [n/a – n/a].
- [56] Perry SL, Leon L, Hoffmann KQ, Kade MJ, Priftis D, Black KA, et al. Chirality-selected phase behaviour in ionic polypeptide complexes. Nat Commun 2015;6:6052. http://dx.doi.org/10.1038/ncomms7052.

- [57] Rabih F, Shamoun AR, Schlenoff JB. Extruded saloplastic polyelectrolyte complexes. Adv Funct Mater 2012;22:1923–31. http://dx.doi.org/10.1002/adfm.201102787.
- [58] Sukhishvili SA, Kharlampieva E, Izumdrudov V. Where polyelectrolyte multilayers and polyelectrolyte complexes meet. Macromolecules 2006;39.
- [59] Antila H, Härkönen M, Sammalkorpi M. Chemistry specificity of DNA-polycation complex salt response: a simulation study of DNA, polylysine and polyethyleneimine. Phys Chem Chem Phys 2015;17:5279–89. <u>http://dx.doi.org/</u> 10.1039/C4CP04967E.
- [60] Meneses-Juárez E, Márquez-Beltrán C, Rivas-Silva JF, Pal U, González-Melchor M. The structure and interaction mechanism of a polyelectrolyte complex: a dissipative particle dynamics study. Soft Matter 2015;11:5889–97. <u>http://dx.doi.org/10.</u> 1039/C5SM00911A.
- [61] Zhang Y, Yildirim E, Antila HS, Valenzuela LD, Sammalkorpi M, Lutkenhaus JL. The influence of ionic strength and mixing ratio on the colloidal stability of PDAC/PSS polyelectrolyte complexes. Soft Matter 2015;11:7392–401. <u>http://dx.doi.org/10.</u> 1039/C5SM01184A.
- [62] Peng B, Muthukumar M. Modeling competitive substitution in a polyelectrolyte complex. J Chem Phys 2015;143:243133. http://dx.doi.org/10.1063/1.4936256.
- [63] Antila HS, Sammalkorpi M. Polyelectrolyte decomplexation via addition of salt: charge correlation driven zipper. J Phys Chem B 2014;118:3226–34. <u>http://dx.doi.org/10.1021/jp4124293</u>.
- [64] Lazutin AA, Semenov AN, Vasilevskaya VV. Polyelectrolyte complexes consisting of macromolecules with varied stiffness: computer simulation. Macromol Theory Simul 2012;21:328–39. http://dx.doi.org/10.1002/mats.201100097.
- [65] Hoda N, Larson RG. Explicit- and implicit-solvent molecular dynamics simulations of complex formation between polycations and polyanions. Macromolecules 2009; 42:8851–63. <u>http://dx.doi.org/10.1021/ma901632c</u>.
- [66] Ou Z, Muthukumar M. Entropy and enthalpy of polyelectrolyte complexation: Langevin dynamics simulations. J Chem Phys 2006;124:154902. <u>http://dx.doi.org/</u> 10.1063/1.2178803.
- [67] Elder RM, Jayaraman A. Molecular simulations of polycation–DNA binding exploring the effect of peptide chemistry and sequence in nuclear localization sequence based polycations. J Phys Chem B 2013;117:11988–99. <u>http://dx.doi.org/10.1021/</u> jp406875a.
- [68] Elder RM, Emrick T, Jayaraman a. Understanding the effect of polylysine architecture on DNA binding using molecular dynamics simulations. Biomacromolecules 2011;12:3870–9. http://dx.doi.org/10.1021/bm201113y.
- [69] Li YJ, Dubin PL, Havel HA, Edwards SL, Dautzenberg H. Complex-formation between polyelectrolyte and oppositely charged mixed micelles—soluble complexes vs coacervation. Langmuir 1995;11:2486–92. <u>http://dx.doi.org/10.1021/</u> la00007a029.
- [70] Hammond PT. Form and function in multilayer assembly: new applications at the nanoscale. Adv Mater 2004;16:1271–93. <u>http://dx.doi.org/10.1002/adma.</u> 200400760.
- [71] Vidyasagar A, Sung C, Gamble R, Lutkenhaus JL. Thermal transitions in dry and hydrated layer-by-layer assemblies exhibiting linear and exponential growth. ACS Nano 2012;6:6174–84. http://dx.doi.org/10.1021/nn301526b.
- [72] Salehi A, Desai PS, Li J, Steele CA, Larson RG. Relationship between polyelectrolyte bulk complexation and kinetics of their layer-by-layer assembly. Macromolecules 2015;48:400–9. http://dx.doi.org/10.1021/ma502273a.
- [73] Castelnovo M, Joanny J-F. Formation of polyelectrolyte multilayers. Langmuir 2000; 16:7524–32. http://dx.doi.org/10.1021/la000211h.
- [74] Kabanov AV, Kabanov VA. DNA complexes with polycations for the delivery of genetic material into cells. Bioconjug Chem 1995;6:7–20. <u>http://dx.doi.org/10.1021/</u> bc00031a002.
- [75] Michaeli I, Overbeek JThG, Voorn MJ. Phase separation of polyelectrolyte solutions. J Polym Sci 1957;23:443–50.
- [76] Tainaka K-I. Effect of counterions on complex coacervation. Biopolymers 1980;19: 1289–98. http://dx.doi.org/10.1002/bip.1980.360190705.
- [77] McQuarrie DA. Statistical mechanics. Sausalito, CA: University Science Books; 2000.
- [78] Hansen JP, McDonald IR. Theory of simple liquids. Boston, MA: Elsevier; 2006.
- [79] Qin J, Priftis D, Farina R, Perry SL, Leon L, Whitmer J, et al. Interfacial tension of polyelectrolyte complex coacervate phases. ACS Macro Lett 2014;3:565–8. <u>http://dx.</u> doi.org/10.1021/mz500190w.
- [80] Priftis D, Xia X, Margossian KO, Perry SL, Leon L, Qin J, et al. Ternary, tunable polyelectrolyte complex fluids driven by complex coacervation. Macromolecules 2014; 47:3076–85. http://dx.doi.org/10.1021/ma500245j.
- [81] Jha PK, Desai PS, Li J, Larson RG. pH and salt effects on the associative phase separation of oppositely charged polyelectrolytes. Polymers (Basel, Switz) 2014;6: 1414–36. <u>http://dx.doi.org/10.3390/polym6051414</u>.
- [82] Biesheuvel PM, Cohen Stuart MA. Electrostatic free energy of weakly charged macromolecules in solution and intermacromolecular complexes consisting of oppositely charged polymers. Langmuir 2004;20:2785–91. <u>http://dx.doi.org/10.1021/</u> la036204l.
- [83] Helfand E, Tagami Y. Theory of the interface between immiscible polymers II. J Chem Phys 1972;56:3592–601. http://dx.doi.org/10.1063/1.1677735.
- [84] Fredrickson GH. The equilibrium theory of inhomogeneous polymers. Oxford: Oxford University Press; 2006.
 [85] Edwards SF. The theory of polymer solutions at intermediate concentration. Proc
- Phys Soc 1966;88:265–80. http://dx.doi.org/10.1088/0370-1328/88/2/301. [86] Edwards SF. The statistical mechanics of polymers with excluded volume. Proc
- Phys Soc 1965;85:613–24. http://dx.doi.org/10.1088/0370-1328/85/4/301.
- [87] Nakamura I, Wang Z-G. Salt-doped block copolymers: ion distribution, domain spacing and effective χ parameter. Soft Matter 2012;8:9356. <u>http://dx.doi.org/10.</u> 1039/c2sm25606a.

- [88] Wang Q, Taniguchi T, Fredrickson GH. Self-consistent field theory of polyelectrolyte systems. J Phys Chem B 2004;108:6733–44. http://dx.doi.org/10.1021/jp037053y.
- [89] De Gennes PG. Scaling concepts in polymer physics. Ithaca: Cornell University Press: 1979
- [90] Sing CE, Olvera de la Cruz M. Polyelectrolyte blends and nontrivial behavior in effective Flory-Huggins parameters. ACS Macro Lett 2014:698–702. <u>http://dx.doi.org/10.1021/mz500202n</u>.
- [91] Leibler L. Theory of microphase separation in block copolymers. Macromolecules 1980;13:1602–17. http://dx.doi.org/10.1021/ma60078a047.
- [92] Fredrickson GH. Computational field theory of polymers: opportunities and challenges. Soft Matter 2007;3:1329. http://dx.doi.org/10.1039/b710604a.
- [93] Bates FS, Fredrickson GH. Block copolymer thermodynamics: theory and experiment. Annu Rev Phys Chem 1990;41:525–57. <u>http://dx.doi.org/10.1146/annurev.</u> physchem.41.1.525.
- [94] Netz RR, Orland. Beyond Poisson–Boltzmann: fluctuation effectsand correlation functions. Eur Phys J E 2000;1:203–14. <u>http://dx.doi.org/10.1007/</u> s101890050023.
- [95] Wittmer J, Johner A, Joanny JF. Random and alternating polyampholytes. Europhys Lett 1993;24:263. <u>http://dx.doi.org/10.1209/0295-5075/24/4/005</u>.
 [96] Nakamura I, Balsara NP, Wang Z. Thermodynamics of ion-containing polymer
- [96] Nakamura I, Balsara NP, Wang Z. Thermodynamics of ion-containing polymer blends and block copolymers. Phys Rev Lett 2011;107:1–5. <u>http://dx.doi.org/10.</u> 1103/PhysRevLett.107.198301.
- [97] Wang ZG. Fluctuation in electrolyte solutions: the self energy. Phys Rev E Stat Nonlinear Soft Matter Phys 2010;81:1–12. <u>http://dx.doi.org/10.1103/PhysRevE.81.</u> 021501.
- [98] Borue VY, Erukhimovich IY. A statistical-theory of globular polyelectrolyte complexes. Macromolecules 1990;23:3625–32. <u>http://dx.doi.org/10.1021/</u> ma00217a015.
- [99] Solis FJ, de la Cruz MO. Collapse of flexible polyelectrolytes in multivalent salt solutions. J Chem Phys 2000;112:2030–5. http://dx.doi.org/10.1063/1.480763.
- [100] Shklovskii Bl. Wigner crystal model of counterion induced bundle formation of rodlike polyelectrolytes. Phys Rev Lett 1999;82:3268–71. <u>http://dx.doi.org/10.1103/</u> PhysRevLett.82.3268.
- [101] de la Cruz MO, Belloni L, Delsanti M, Dalbiez JP, Spalla O, Drifford M. Precipitation of highly-charged polyelectrolyte solutions in the presence of multivalent salts. J Chem Phys 1995;103:5781–91. http://dx.doi.org/10.1063/1.470459.
- [102] Raspaud E, Olvera de la Cruz M, Sikorav JL, Livolant F. Precipitation of DNA by polyamines: a polyelectrolyte behavior. Biophys J 1998;74:381–93. <u>http://dx.doi.org/</u> 10.1016/S0006-3495(98)77795-1.
- [103] Nyquist RM, Ha BY, Liu AJ. Counterion condensation in solutions of rigid polyelectrolytes. Macromolecules 1999;32:3481–7. <u>http://dx.doi.org/10.1021/</u> ma9811021.
- [104] Muthukumar M. Theory of counter-ion condensation on flexible polyelectrolytes: adsorption mechanism. J Chem Phys 2004;120:9343–50. <u>http://dx.doi.org/10. 1063/1.1701839.</u>
- [105] Liu S, Muthukumar M. Langevin dynamics simulation of counterion distribution around isolated flexible polyelectrolyte chains. J Chem Phys 2002;116:9975. http://dx.doi.org/10.1063/1.1476930.
- [106] Muthukumar M, Hua J, Kundagrami A. Charge regularization in phase separating polyelectrolyte solutions. J Chem Phys 2010;132. <u>http://dx.doi.org/10.1063/1.</u> 3328821.
- [107] Chu H, Gao J, Chen C-W, Huard J, Wang Y. Injectable fibroblast growth factor-2 coacervate for persistent angiogenesis. Proc Natl Acad Sci U S A 2011;108:13444–9. http://dx.doi.org/10.1073/pnas.1110121108.
- [108] Hwang DS, Waite JH, Tirrell M. Promotion of osteoblast proliferation on complex coacervation-based hyaluronic acid—recombinant mussel adhesive protein coatings on titanium. Biomaterials 2010;31:1080–4. <u>http://dx.doi.org/10.1016/j.biomaterials.2009.10.041</u>.
- [109] Vidyasagar A, Sung C, Losensky K, Lutkenhaus JL. PH-dependent thermal transitions in hydrated layer-by-layer assemblies containing weak polyelectrolytes. Macromolecules 2012;45:9169–76. http://dx.doi.org/10.1021/ma3020454.
- [110] Sung C, Hearn K, Lutkenhaus J. Thermal transitions in hydrated layer-by-layer assemblies observed using electrochemical impedance spectroscopy. Soft Matter 2014;10:6467–76. http://dx.doi.org/10.1039/C4SM01269K.
- [111] Köhler K, Möhwald H, Sukhorukov GB. Thermal behavior of polyelectrolyte multilayer microcapsules: 2. Insight into molecular mechanisms for the PDADMAC/PSS system. J Phys Chem B 2006;110:24002–10. http://dx.doi.org/10.1021/jp062907a.
- [112] Lutkenhaus JL, Hrabak KD, McEnnis K, Hammond PT. Elastomeric flexible freestanding hydrogen-bonded nanoscale assemblies. J Am Chem Soc 2005;127: 17228–34. http://dx.doi.org/10.1021/ja053472s.
- [113] Hamley IW. Liquid crystal phase formation by biopolymers. Soft Matter 2010;6: 1863–71. http://dx.doi.org/10.1039/b923942a.
- [114] Dormidontova EE. Role of competitive PEO-water and water-water hydrogen bonding in acqueous solution PEO behavior. Macromolecules 2002;35:987.
- [115] Perry SL, Li Y, Priftis D, Leon L, Tirrell M. The effect of salt on the complex coacervation of vinyl polyelectrolytes. Polymers (Basel, Switz) 2014;6:1756–72. <u>http://dx.</u> doi.org/10.3390/polym6061756.
- [116] Priftis D, Tirrell M. Phase behaviour and complex coacervation of aqueous polypeptide solutions. Soft Matter 2012;8:9396. http://dx.doi.org/10.1039/c2sm25604e.
- [117] Chollakup R, Beck JB, Dirnberger K, Tirrell M, Eisenbach CD. Polyelectrolyte molecular weight and salt effects on the phase behavior and coacervation of aqueous solutions of poly(acrylic acid) sodium salt and poly(allylamine) hydrochloride. Macromolecules 2013;46:2376–90. http://dx.doi.org/10.1021/ma202172q.
- [118] Priftis D, Laugel N, Tirrell M. Thermodynamic characterization of polypeptide complex coacervation. Langmuir 2012;28:15947–57. <u>http://dx.doi.org/10.1021/</u> la302729r.

- [119] Salis A, Ninham BW. Models and mechanisms of Hofmeister effects in electrolyte solutions, and colloid and protein systems revisited. Chem Soc Rev 2014;43: 7358–77. http://dx.doi.org/10.1039/c4cs00144c.
- [120] Netz RR, Horinek D. Progress in modeling of ion effects at the vapor/water interface. Annu Rev Phys Chem 2012;63:401–18. <u>http://dx.doi.org/10.1146/annurevphyschem-032511-143813</u>.
- [121] Ghostine R a, Shamoun RF, Schlenoff JB. Doping and diffusion in an extruded saloplastic polyelectrolyte complex. Macromolecules 2013;46:4089–94. <u>http://dx.</u> doi.org/10.1021/ma4004083.
- [122] Perry SL, Sing CE. PRISM-based theory of complex coacervation: excluded volume versus chain correlation. Macromolecules 2015;48:5040–53. <u>http://dx.doi.org/10.</u> 1021/acs.macromol.5b01027.
- [123] Bates FS, Hillmyer MA, Lodge TP, Bates CM, Delaney KT, Fredrickson GH. Multiblock polymers: panacea or Pandora's box? Science 2012;336:434–40. <u>http://dx.doi.org/</u> 10.1126/science.1215368.
- [124] Kumar R, Audus D, Fredrickson GH. Phase separation in symmetric mixtures of oppositely charged rodlike polyelectrolytes. J Phys Chem B 2010;114:9956–76. <u>http://</u> dx.doi.org/10.1021/jp101413a.
- [125] Muthukumar M. Pattern recognition by polyelectrolytes. J Chem Phys 1995;103: 4723–31. http://dx.doi.org/10.1063/1.470691.
- [126] Manning GS. Limiting laws and counterion condensation in polyelectroyte solutions. I Colligative properties. J Chem Phys 1969;51:924–33. <u>http://dx.doi.org/10. 1063/1.1672157.</u>
- [127] Zhang R, Shklovskii Bl. Phase diagram of solution of oppositely charged polyelectrolytes. Physica A 2005;352:216–38. http://dx.doi.org/10.1016/j.physa.2004.12.037.
- [128] Dias RS, Linse P, Pais AACC. Stepwise disproportionation in polyelectrolyte complexes. J Comput Chem 2011;32:2697–707. http://dx.doi.org/10.1002/jcc.21851.
- [129] Klos JS, Sommer JU. Simulation of complexes between a charged dendrimer and a linear polyelectrolyte with finite rigidity. Macromol Theory Simul 2012;21:448–60. http://dx.doi.org/10.1002/mats.201100120.
- [130] Potemkin II, Palyulin VV. Complexation of oppositely charged polyelectrolytes: effect of discrete charge distribution along the chain. Phys Rev E 2010;81:041802. http://dx.doi.org/10.1103/PhysRevE.81.041802.
- [131] Kłos JS, Sommer J-U. Monte Carlo simulations of charged dendrimer-linear polyelectrolyte complexes and explicit counterions. J Chem Phys 2011;134:204902. http://dx.doi.org/10.1063/1.3592558.
- [132] Derouchey J, Netz RR, R\u00e4dler JO. Structural investigations of DNA-polycation complexes. Eur Phys J E 2005;16:17–28. <u>http://dx.doi.org/10.1140/epje/e2005-00003-4</u>.
- [133] Ziebarth J, Wang Y. Molecular dynamics simulations of DNA–polycation complex formation. Biophys J 2009;97:1971–83. http://dx.doi.org/10.1016/j.bpj.2009.03.069.
- [134] Hoffmann KQ, Perry SL, Leon L, Priftis D, Tirrell M, de Pablo JJ. A molecular view of the role of chirality in charge-driven polypeptide complexation. Soft Matter 2015; 11:1525–38. http://dx.doi.org/10.1039/C4SM02336F.
- [135] Fu J, Schlenoff JB. Driving forces for oppositely charged polyion association in aqueous solutions: enthalpic, entropic, but not electrostatic. J Am Chem Soc 2016;138: 980–90. http://dx.doi.org/10.1021/jacs.5b11878.
- [136] Fisher ME, Levin Y. Criticality in ionic fluids: Debye-Hückel theory, Bjerrum, and beyond. Phys Rev Lett 1993;71:3826–9. <u>http://dx.doi.org/10.1103/PhysRevLett.</u> 71.3826.
- [137] Aqua JN, Banerjee S, Fisher ME. Criticality in charge-asymmetric hard-sphere ionic fluids. Phys Rev E Stat Nonlinear Soft Matter Phys 2005;72:1–23. <u>http://dx.doi.org/</u> 10.1103/PhysRevE.72.041501.
- [138] Hayes R, Warr GG, Atkin R. Structure and nanostructure in ionic liquids. Chem Rev 2015;115:6357–426. http://dx.doi.org/10.1021/cr500411q.
- [139] Riggleman RA, Kumar R, Fredrickson GH. Investigation of the interfacial tension of complex coacervates using field-theoretic simulations. J Chem Phys 2012;136: 1–12. http://dx.doi.org/10.1063/1.3674305.
- [140] Riggleman RA, Fredrickson GH. Field-theoretic simulations in the Gibbs ensemble. J Chem Phys 2010;132:024104. http://dx.doi.org/10.1063/1.3292004.
- [141] Popov YO, Lee J, Fredrickson GH. Field-theoretic simulations of polyelectrolyte complexation. J Polym Sci B 2007;45:3223–30. <u>http://dx.doi.org/10.1002/polb.</u> 21334.
- [142] Lee J, Popov YO, Fredrickson GH. Complex coacervation: a field theoretic simulation study of polyelectrolyte complexation. J Chem Phys 2008;128:1–13. <u>http://dx.doi.org/10.1063/1.2936834</u>.
- [143] Pryamitsyn V, Ganesan V. Interplay between depletion and electrostatic interactions in polyelectrolyte-nanoparticle systems. Macromolecules 2014;47: 6095-112. http://dx.doi.org/10.1021/ma501014u.
- [144] Fredrickson GH, Ganesan V, Drolet F. Field-theoretic computer simulation methods for polymers and complex fluids. Macromolecules 2002;35:16–39. <u>http://dx.doi.org/10.1021/ma011515t</u>.
- [145] Kumar R, Muthukumar M. Microphase separation in polyelectrolytic diblock copolymer melt: weak segregation limit. J Chem Phys 2007;126:0–12. <u>http://dx.doi.org/</u> 10.1063/1.2737049.
- [146] Yang S, Vishnyakov A, Neimark AV. Self-assembly in block polyelectrolytes. J Chem Phys 2011;134:0–8. http://dx.doi.org/10.1063/1.3532831.
- [147] Sing CE, Zwanikken JW, Olvera de la Cruz M. Electrostatic control of block copolymer morphology. Nat Mater 2014;13:694–8. <u>http://dx.doi.org/10.1038/</u> nmat4001.
- [148] Sing CE, Zwanikken JW, de la Cruz MO. Theory of melt polyelectrolyte blends and block copolymers: phase behavior, surface tension, and microphase periodicity. J Chem Phys 2015;142:034902. http://dx.doi.org/10.1063/1.4905830.
- [149] Alexander-Katz A, Moreira AG, Sides SW, Fredrickson GH. Field-theoretic simulations of polymer solutions: finite-size and discretization effects. J Chem Phys 2005;122:0–8. http://dx.doi.org/10.1063/1.1827211.

- [150] Alexander-Katz A, Moreira AG, Fredrickson GH. Field-theoretic simulations of confined polymer solutions. J Chem Phys 2003;118:9030–6. <u>http://dx.doi.org/10.1063/</u> 1.1567257.
- [151] Alexander-Katz A, Fredrickson GH. Diblock copolymer thin films: a field-theoretic simulation study. Macromolecules 2007;40:4075–87. <u>http://dx.doi.org/10.1021/</u> ma070005h.
- [152] Koski J, Chao H, Riggleman RA. Field theoretic simulations of polymer nanocomposites. J Chem Phys 2013;139. http://dx.doi.org/10.1063/1.4853755.
- [153] Yildirim E, Zhang Y, Lutkenhaus JL, Sammalkorpi M. Thermal transitions in polyelectrolyte assemblies occur via a dehydration mechanism; 2015. <u>http://dx.doi.org/10.1021/acsmacrolett.5b00351</u>.
- [154] Geissler PL. Water interfaces, solvation, and spectroscopy. Annu Rev Phys Chem 2013;64:317–37. http://dx.doi.org/10.1146/annurev-physchem-040412-110153.
- [155] Ceriotti M, Cuny J, Parrinello M, Manolopoulos DE. Nuclear quantum effects and hydrogen bond fluctuations in water. Proc Natl Acad Sci U S A 2013;110:15591–6. http://dx.doi.org/10.1073/pnas.1308560110.
- [156] Schweizer KS, Gurro JG. Integral equation theories of the structure, thermodynamics, and phase transitions of polymer fluids. 1997;98. <u>http://dx.doi.org/10.1002/</u> 9780470141571.ch1.
- [157] Schweizer KS, Curro JG. Integral-equation theory of the structure of polymer melts. Phys Rev Lett 1987;58:246–9. http://dx.doi.org/10.1103/PhysRevLett.58.246.
 [158] Zwanikken JW, Jha PK, De La Cruz MO. A practical integral equation for the struc-
- [158] Zwanikken JW, Jha PK, De La Cruz MO. A practical integral equation for the structure and thermodynamics of hard sphere Coulomb fluids. J Chem Phys 2011;135: 1–7. http://dx.doi.org/10.1063/1.3624809.
- [159] Zwanikken JW, de la Cruz MO. Tunable soft structure in charged fluids confined by dielectric interfaces. Proc Natl Acad Sci 2013;110:5301–8. <u>http://dx.doi.org/10.</u> 1073/pnas.1302406110.
- [160] Kjellander R, Kjellander R, Celja SM, Celja SM. Inhomogeneous Coulomb fluids with image interactions between planar surfaces. I. J Chem Phys 1984;82:2122. <u>http://</u> dx.doi.org/10.1063/1.448350.
- [161] Sing CE, Zwanikken JW, de la Cruz MO. Effect of ion-ion correlations on polyelectrolyte gel collapse and reentrant swelling. Macromolecules 2013;46:5053–65. http://dx.doi.org/10.1021/ma400372p.

- [162] Sing CE, Zwanikken JW, de la Cruz MO. Interfacial behavior in polyelectrolyte blends: hybrid liquid-state integral equation and self-consistent field theory study. Phys Rev Lett 2013;111:168303. <u>http://dx.doi.org/10.1103/PhysRevLett.</u> 111.168303.
- [163] Sing CE, Zwanikken JW, Olvera De La Cruz M. Ion correlation-induced phase separation in polyelectrolyte blends. ACS Macro Lett 2013;2:1042–6. <u>http://dx.doi.org/</u> 10.1021/mz400511r.
- [164] Longo CS, de la Cruz MO, Szleifer I. Molecular theory of weak polyelectrolyte thin films. Soft Matter 2012;8:1344–54. http://dx.doi.org/10.1039/C1SM06708G.
 [165] Longo GS, Olvera de la Cruz M, Szleifer I. pH-controlled nanoaggregation in amphi-
- [165] Longo GS, Olvera de la Cruz M, Szleiter I. pH-controlled nanoaggregation in amphiphilic polymer co-networks. ACS Nano 2013;7:2693–704.
- [166] Daoulas KC, Müller M. Single chain in mean field simulations: quasi-instantaneous field approximation and quantitative comparison with Monte Carlo simulations. J Chem Phys 2006;125:184904. <u>http://dx.doi.org/10.1063/1.2364506</u>.
 [167] Detcheverry FA, Pike DQ, Nealey PF, Müller M, de Pablo JJ. Monte Carlo simulation
- [167] Detcheverry FA, Pike DQ, Nealey PF, Müller M, de Pablo JJ. Monte Carlo simulation of coarse grain polymeric systems. Phys Rev Lett 2009;102:197801. <u>http://dx.doi.org/10.1103/PhysRevLett.102.197801</u>.
- [168] Rubinstein M, Semenov AN. Dynamics of entangled solutions of associating polymers. Macromolecules 2001;34:1058–68. <u>http://dx.doi.org/10.1021/</u> ma0013049.
- [169] Sing MK, Wang Z-G, McKinley GH, Olsen BD. Celebrating soft matter's 10th anniversary: chain configuration and rate-dependent mechanical properties in transient networks. Soft Matter 2015;00:1–12. http://dx.doi.org/10.1039/c4sm02181a.
- [170] Tanaka F, Edwards SF. Viscoelastic properties of physically crosslinked networks. T. Transient network theory viscoelastic properties of physically cross-linked networks. Transient network theory. Macromolecules 2002;25:1516–23. <u>http://dx. doi.org/10.1021/ma00031a024</u>.
- [171] Castelnovo M, Joanny J. Phase diagram of diblock polyampholyte solutions. Macromolecules 2002;4531–8. http://dx.doi.org/10.1021/ma012097v.