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Depletion interactions operate in aqueous solutions of globular proteins and polymers and are often thought to be one of the causes of liquid–liquid phase separation.[1] From a theoretical standpoint, such a phase separation is a complex issue bound to be sensitive to the nature of the various particle interactions which, unfortunately, are not known precisely. In attempting to come to terms with this, one may distinguish an important subclass of amenable problems, namely, the behavior of one spherical protein immersed in a semidilute polymer solution. An important simplification arises when the radius a of the sphere is smaller than the polymer correlation length ξ. This has been taken advantage of in several theoretical works.[2–5] Nevertheless, one important topic has not been treated. It is how the interaction V_{sp} between the particle and a polymer segment affects the polymer distribution in the depletion volume.

We wish to compute the density $\psi^2(\vec{r})$ of segments surrounding the sphere whose center is placed at the origin of our Cartesian coordinate system $\vec{r} = (x, y, z)$. If a potential V is exerted on a segment of Kuhn length A, the density satisfies an eigenvalue equation[6]

$$\mu\psi - \frac{1}{6}A^2\Delta\psi + \left(\frac{V}{k_B T}\right)\psi = 0 \qquad (1)$$

Here, μ is an eigenvalue, k_B is Boltzmann's constant, and T is the temperature. Equation 1 has been used to study depletion before.[7] The polymer solution is supposed semidilute although, here, $V(\vec{r})$ consists of two parts: not only the self-consistent potential[8] V_{SCF} among segments, which is proportional to the density $\psi^2(\vec{r})$ for a good solvent, but also the interaction V_{sp} between the sphere and a polymer segment. The term containing the Laplacian Δ arises from confining the polymer chains, in our case within the depletion layer around the spherical particle. At its hard surface, the density must vanish, whereas it tends to C_0, the bulk density of segments, far away from the sphere. The eigenvalue is determined from the latter requirement. We now rewrite eq 1

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(3) Abbott, N. L.; Blankschtein, D.; Hatton, T. A. *Macromolecules* **1992**, *25*, 5192.
(4) Odijk, T. *Macromolecules* **1996**, *29*, 1842.
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$$\Delta f - \left(\frac{6 V_{sp}}{A^2 k_B T}\right)f + \xi^{-2}(f - f^3) = 0 \qquad (2)$$

in terms of the dimensionless variable $f(\vec{r}) \equiv C_0^{-1/2}\psi(\vec{r})$ and a correlation length[8] ξ proportional to $C_0^{-1/2}$. (Boundary conditions $f = 0$ at $r = a$; $f = 1$ at $r = \infty$.) Next, it is plausible to investigate the deletion of the third term[4,5] for small spheres.

Let us suppose both the spherical radius a and the typical range λ of the potential V_{sp} are smaller than the correlation length ξ. It is then useful to replace eq 2 by the following zero-order boundary value problem

$$\frac{1}{R^2}\frac{d}{dR}\left(R^2\frac{df_0}{dR}\right) = uf_0 \qquad (3)$$

with $f_0 = 0$ at $R = 1$, $f_0 = 1$ as $R \to \infty$, and $u \equiv 6a^2 V_{sp}/A^2 k_B T$; a rescaled radial coordinate, $R \equiv r/a$ has been introduced, for convenience. Equation 3 is certainly valid to the leading order for $R < \xi/(\lambda + a)$. Moreover, the third term in eq 2 is fortunately a second-order perturbation and regular as well whenever a/ξ and λ/ξ are both smaller than unity. Hence, eq 3 is uniformly valid to the leading order in the entire region $1 < R < \infty$. A similar line of reasoning has been used previously in refs 4 and 5 in the ideal case $V_{sp} \equiv 0$. In particular, lengthy arguments have been adduced for the legitimacy of the Laplace equation (eq 3 with $V_{sp} \equiv 0$) beyond the mean-field approximation.[5] In a similar vein, we expect eq 3 to remain useful under the conditions stated, even when segment fluctuations render qualitatively useless the third term in eq 2. There is thus a depletion volume given by eq 3; well beyond this volume, there is a sea of strongly fluctuating segments for which mean-field arguments are poor.[5]

We next solve eq 3 for a general u which is impossible to do exactly. A naive WKB approximation presupposing a large enough u is, however, out of the question because depletion persists somewhat beyond the range λ; so we have to confront the difficulty that $f_0 < 1$ as $u \simeq 0$. Historically, the Langer substitution[9] ($R \equiv \exp t$; $g(t) \equiv e^{t/2}f_0(e^t)$) has been of considerable use in devising uniform semiclassical approximations to the radial Schrödinger equation[10] and turns out to be sensible for the current depletion problem as well.

$$\frac{d^2 g}{dt^2} = wg \qquad (4)$$

$$w \equiv e^{2t}u + \frac{1}{4} \qquad (5)$$

The constant $1/4$ ensures that g has the right behavior at infinity and retains the correct depletion structure as u vanishes beyond λ. Of course, the following WKB solution[11] is only semiquantitatively correct

$$g = c_1 w^{-1/4}(t)e^{\int_0^t ds\, w^{1/2}(s)} + c_2 w^{-1/4}(t)e^{-\int_0^t ds\, w^{1/2}(s)} \qquad (6)$$

Eliminating the constants c_1 and c_2 by imposing the two

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(10) Berry, M. V.; Mount, K. E. *Rep. Prog. Phys.* **1972**, *35*, 315.
(11) Bender, C. M.; Orszag, S. A. *Advanced Mathematical Methods for Scientists and Engineers*; McGraw-Hill: New York, 1978.

boundary conditions and reverting to the original variables, we attain the solution

$$f_0 = \frac{2^{1/2}e^{-J}\sinh I(R)}{R^{1/2}(R^2 u(R) + {}^1/_4)^{1/4}} \qquad (7)$$

$$J \equiv \int_1^\infty dy \, \frac{u(y)}{\left(u(y) + \dfrac{1}{4y^2}\right)^{1/2} + \dfrac{1}{2y}} \qquad (8)$$

$$I(R) \equiv \int_1^R dy \left(u(y) + \frac{1}{4y^2}\right)^{1/2} \qquad (9)$$

At this stage, it is important to mention the requirements on $u(y)$. First, there may be no turning points: $w > 0$ or $V_{sp}(r) > -k_B T A^2/24r^2$, a condition that leaves room for the existence of weak attractive potentials. Second, if repulsive, the potential must decay faster than r^{-2}.

Knowing the segment distribution $\psi^2 \simeq C_0 f_0^2$, we may write the free energy of depletion in the form

$$U_d = h\xi^{-4/3} \int_{|\vec{r}|>a} d\vec{r} \left[k_B T(\vec{\nabla}f_0)^2 + \left(\frac{6V_{sp}}{A^2}\right)f_0^2 \right] \quad (10)$$

In effect, minimization of U_d should yield eq 3. Furthermore, U_d must be proportional to the number of segments depleted from the depletion volume and this number is proportional to C_0. Within scaling theory,[7] the correlation length ξ scales as $C_0^{-3/4}$. As argued above and in previous work,[5] we prefer scaling to mean-field theory at this juncture, in order to account for the correlations in the reservoir of semidilute polymer. The unknown coefficient h has dimension length to the power one-third.

We illustrate the above computations in a case when the depletion volume is determined by one sole scale b. Then, the free energy of depletion should scale simply as

$$U_d \simeq \left(\frac{b}{\xi}\right)^{4/3} k_B T \qquad \xi > b \qquad (11)$$

in analogy with arguments advanced by de Gennes.[2] Let the polymer and the protein both be negatively charged and the protein−segment interaction be given by a screened form

$$V_{sp}/k_B T \simeq \frac{Z_{eff}A}{(1 + \kappa a)r} e^{-\kappa(r-a)} \qquad (12)$$

The protein sphere may be viewed as bearing Z_{eff} renormalized charges.[12] The concentration of excess salt determines the Debye length κ^{-1}. The semidilute polyelectrolyte[13] is assumed to be strongly charged with an effective spacing of about one elementary charge per Bjerrum length. The function $u \equiv B\exp{-\eta y}/y$ with $B \equiv 6Z_{eff}a/A(1 + \kappa a)\exp(-\kappa a)$, $\eta \equiv \kappa a$ and $y \equiv r/a$, is inserted in eqs 7−9. Note that generally $B \gg 1$. Inspection of the behavior of the function f_0 given by eq 7 shows that a scaled depletion radius R_* may be defined by

$$K(R_*) \equiv \int_{R_*}^\infty dy \, \frac{u}{\left(u + \dfrac{1}{4y^2}\right)^{1/2} + \dfrac{1}{2y}} = \mathcal{O}(1) \qquad (13)$$

for I may be rewritten as

$$I(R_*) = \frac{1}{2}\ln R_* + J - K(R_*) \qquad (14)$$

For the problem at hand, we remark that the integrand in eq 13 may be bounded by a variety of functions. It is then easy to show that

$$R_* \simeq \eta^{-1}\ln\frac{B}{\eta} \qquad (15)$$

to the leading order. We finally arrive at the total depletion radius

$$b \simeq a + \kappa^{-1}\ln\frac{6Z_{eff}}{A\kappa(1 + \kappa a)} \qquad (16)$$

In eq 11, b and ξ are antagonistic scales as far as the ionic strength is concerned, for ξ is given by[13]

$$\xi \simeq A(\kappa)^{-1/4}\kappa^{1/4}(A_0 c_0)^{-3/4} \qquad (17)$$

The Kuhn length $A = A(\kappa)$ increases with decreasing salt[13] ($A_0 = A(\infty)$). Accordingly, we have a rather crude criterion for the onset of phase separation

$$b \simeq \xi \qquad (18)$$

In that case, the depletion energy of a protein is of the order of its kinetic energy so the charged sphere would like to enter an environment free from polymer.

For a general interaction, we are hampered by a lack of knowing the unknown variable h in eq 10. Still, a standard perturbation treatment[14] is possible for sufficiently weak potentials. In the reference state ($V_{sp} = 0$), the coefficient h should be $\mathcal{O}(a^{1/3})$ and the solution to the Laplace equation (eq 3 with $u = 0$) is $1 - (a/r)$. Accordingly, perturbation theory yields

$$U_d \simeq \left(\frac{a}{\xi}\right)^{4/3}\left(k_B T + \frac{6}{A^2 a}\int_{|\vec{r}|>a} d\vec{r} \, V_{sp}(\vec{r})\left(1 - \frac{a}{r}\right)^2\right) \qquad (19)$$

By way of illustration, suppose the potential is attractive and of the form

$$V_{sp} = -\epsilon k_B T \qquad a < r < a + \Delta \qquad (20)$$

with $\epsilon \ll 1$ and a range $\Delta = \mathcal{O}(a)$ or smaller. Then, eq 19 gives

$$U_d \simeq \left(\frac{a}{\xi}\right)^{4/3}\left(1 - \frac{2\epsilon\Delta^3}{A^2 a}\right)k_B T \qquad (21)$$

This result should be compared with several estimates discussed by Abbott et al.[3]

The interaction of a protein with other types of semidilute gels is also of interest, especially in biology. A recent work[15] extends Ogston's classical analysis[16] on the partitioning of spheres in networks of random rods to the charged case.

In summary a WKB theory has been given of the polymer distribution surrounding a small protein sphere. It is stressed that it is not a mean-field theory, for segment correlations are incorporated in the front factor of the depletion free energy (eq 10). Our derivation of the linear

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equation (3) starting from a self-consistent approximation given by eq 1 is merely heuristic. Such a linear equation must obtain even when segment correlations are adequately accounted for.[5] Simple linearity arises because the protein is a small particle: there is a depletion region surrounding the sphere of restricted dimensions, where the distribution of segments varies markedly. Sometimes, as in the case when protein and polymer are both charged, it may be possible and convenient to introduce an effective total depletion radius *b* (see eq 16). But such a simplification is not always viable as in the case of weak attractive forces (see eq 21). The results deduced here should be of help in explaining phase-separation phenomena. In particular, eq 18 may be useful in understanding the sensitivity to salt of the isotropic−isotropic separation of suspensions containing charged proteins interacting with a polyelectrolyte of the same sign.

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