Protein–Macromolecule Interactions

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Received September 28, 1995

Although the interactions between proteins and various types of macromolecules are of considerable technological interest,1 little theoretical work has been done that makes use of the fact that proteins are often comparatively small particles. Thus, our interest is in a regime opposite to that focused on in the usual depletion theories.2 Here, a protein will be viewed, perhaps naively, as a small hard sphere whose dielectric permittivity is negligible compared to that of water. Its interaction otherwise with some macromolecular segment density ψ will be inert. Some time ago, de Gennes already presented several, not so widely known, preliminary depletion theories.2 Here, a protein will be viewed, a regime opposite to that focused on in the usual theory—a hybrid approach combining scaling and self-consistent arguments as in the theory of polymer adsorption—would not alter this conclusion. One would require a correlation length ξ ~ c0−3/4 from scaling theory instead of ξ ~ c0−1/2 and hence replace f3 in eq 3 by f4.

We now rederive a previous result3 by way of illustration. We wish to compute the work w expended by inserting a protein sphere in a semidilute solution. Since a and ξ ~ c0−3/4 are the only relevant scales, we have w/kT = h(a/ξ) with h a dimensionless function, k Boltzmann’s constant, and T the temperature. As shown above, a volume of order a3 surrounding the protein, is depleted of a3 c0 segments. Therefore, the number of protein—segment interactions involved in the work w must be proportional to c0 or in other words ξ~−4/3.

Assuming h(x) is a simple power law, we then have

\[ \frac{w}{k_BT} \approx \frac{a^{4/3}}{p} (\xi > a) \]  

Next, the same argument may be used for a small sphere enclosed within a chain of radius5 R ~ Nk−3/4; consisting of Nk Kuhn segments: a3 c0 segments are depleted from the vicinity of the protein; the average segment concentration in the coil is c = Nk−3/4. Hence we obtain

\[ \frac{w}{k_BT} \approx \frac{a^{4/3}}{p} (R > a) \]

for a and R are the relevant scales in this case. The interaction w as such is not so interesting but rather the cross second virial coefficient

\[ \mathcal{B} \equiv B_{2,pm} \approx \frac{1}{2} \int dR \int dR' \int d\mathbf{n}_m (1 - e^{-w(r_p, r_m) k_BT}) \]

given in terms of the system volume V and the potential of mean force \( w(r_p, r_m) \) between the protein centered at \( r_p \) and the macromolecule with center of mass fixed at \( r_m \) and with all configurations integrated out. Since \( w(r_p, r_m) = 0 \) (w) and \( w < k_BT \), eq 7 reduces to

\[ \mathcal{B} \approx \frac{1}{V} \int dR \int dR' \int d\mathbf{n}_m \frac{w}{k_BT} \approx R^{3/2} a^{4/3} (R > a) \]

Accordingly, the cross coefficient is quite small and proportional to Nk which is plausible in retrospect: the interaction between a small, inert object and a long chain is expected to be extensive. Equation 8 should be compared to the analogous coefficient between a short and a long chain discussed by Witten and Prentis.6 The same reasoning applied to a small sphere interacting with an ideal Gaussian coil of radius \( R_o = Nk^{1/2} A_k \) would lead to

\[ \frac{w}{k_BT} \approx \frac{a}{R_o} \]
The excluded-volume effect so we actually attain the ideal chain case given by eq. The segmentsof the displaced section are effectively ideal, with the relatively small size of the protein. If the excluded-volume effect is connected with the excluded-volume arising from the polymer (i.e., \( \beta < A_k^{2/3} \)). There is now a subtlety concerning the excluded-volume parameter \( z_B = \frac{a^3}{2}A_k^{-1/3} \). Sensitive to the chain stiffness and the quality of the polymer (i.e., \( \kappa \)). Often, the chain may be so stiff that the inequality \( P > \kappa^{-1} \). Finally, biofilaments exist for which \( P > 1 \). In the adjoining regime (\( z_B < 1 \)), the interaction between the segments of the displaced section is effectively ideal, and we may retain eq 11, even though the whole chain is expanded by the excluded-volume effect.

\[
\bar{B} \approx N_k A_k^{3/2} (L > a > P; a < A_k^{2/3} \beta^{-1}) \quad (12)
\]

This indeed crosses over to eq 11 when we set \( a = A_k^{2/3} \beta^{-1} \), as it must. It is inferred that the interaction between a protein and a flexible chain is peculiarly sensitive to the chain stiffness and the quality of the solvent. Next, it is straightforward to apply the same argument when the macromolecule is a semiflexible chain of length \( L \), persistence length \( P = 1/2A_k \), and diameter \( D \), for we know that \( \beta = P/D \).

\[
\bar{B} \approx LP^{1/3}D^{2/3}a^{4/3} \quad (L > P > D; a > P^2D^{-1}) \quad (13)
\]

\[
\bar{B} \approx LPa \quad (L > a > P > D; a > P^2D^{-1}) \quad (14)
\]

Often, the chain may be so stiff that the inequality \( P > a > D \) is valid, implying that we view the small sphere as interacting with a thin curve that is effectively straight on the scale of \( a \). Hence, the following simple relation is valid

\[
\bar{B} \approx La^2 \quad (L > P > a > D) \quad (15)
\]

which crosses over to eq 12 at \( a = P \), as it should. Finally, biofilaments exist for which \( P > D > a \) in which case we may write

\[
\bar{B} \approx LD^2 \quad (L > P > D > a) \quad (16)
\]

It is also a matter of quadrature to extend these expressions to the case of a protein interacting with a highly charged polyelectrolyte in excess salt. The correlation length \( \xi \) is given in terms of the total persistence length \( P_t \), the Debye length \( \kappa^{-1} \), and the monomer concentration \( N \), each monomer of length \( A \) bearing one elementary charge. Therefore, the ionic-strength dependence of the protein–polyelectrolyte interaction can be expressed by

\[
\frac{W}{kT} \sim (P_t/k)^{1/3} \sim n_s^{-1/2} \quad (18)
\]

where \( ns \) is the 1:1 electrolyte concentration and \( P_t \) is \( \kappa^{-1} \) at low salt. In dilute solution, the polyelectrolyte is

\[
R \approx L^{35/4}(P_t/k)^{5/3} \quad (19)
\]

so there are four regimes analogous to those for semiflexible chains discussed above

\[
\bar{B} \approx L(P_t/k)^{1/3}a^{4/3} \quad (L > P > \kappa^{-1}; a > P_t^{2/3}k) \quad (20)
\]

\[
\bar{B} \approx LP_t a \quad (L > a > P_t > \kappa^{-1}; a > P_t^{2/3}k) \quad (21)
\]

\[
\bar{B} \approx La^2 \quad (L > P_t > a > \kappa^{-1}) \quad (22)
\]

\[
\bar{B} \approx L\kappa^{-2} \quad (L > P_t > \kappa^{-1} > a) \quad (23)
\]

In the last expression, the exclusion radius is the Debye screening length \( \kappa^{-1} \) because the protein is repelled by the chain via the formation of image charges. \( \kappa \).

**Note Added in Proof:** Recently, Wills et al.\(^{11}\) performed gel chromatography and sedimentation experiments on poly(ethylene glycol) and a substantial number of globular proteins so as to determine the cross coefficient \( \bar{B} \) as a function of the protein radius \( a \). The expression derived by Jansons and Phillips,\(^7\) valid even for large radii, appears to agree with the experimental curve fairly well except for a deviation possibly attributable to eq 11. The peculiar ionic-strength dependence of \( \bar{B} \) described by eqs 20–23 stems from the OSF theory of the persistence length. Note that entropic fluctuations\(^{12}\) will not perturb the scaling nature of these expressions.

**Acknowledgment.** I thank J. A. M. Smit (University of Leiden) and D. W. de Bruijne (Unilever Research Vlaardingen) for organizing several discussions.

**References and Notes**