A Kinetic Model of Protein Adsorption/Surface-Induced Transition Kinetics Evaluated by the Scaled Particle Theory

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I. INTRODUCTION

The adsorption of proteins and other large molecules at the liquid-solid interface often involves a surface-induced transition in either internal conformation or molecular orientation. Recently, Van Tassel et al. modeled this adsorption/transition process as the sequential surface placement of spreading disks. In this work, we employ the scaled particle theory (SPT) to derive approximate analytical expressions for the probability functions appearing in the kinetic equations for this model system. Specifically, the probability functions governing the adsorption and spreading events are calculated in terms of the reversible work required to create cavities in a binary system of spread and unspread disks. Compared to those derived earlier via a density expansion theory (DET), the SPT approximated probability functions are simpler and more accurate (compared to simulation), and are applicable over a wider set of parameter values. © 1999 Academic Press

Key Words: protein adsorption; surface-induced transition; kinetic model; scaled particle theory.

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I. INTRODUCTION

The adsorption of proteins and other macromolecules at the liquid–solid interface often exhibits features that are irreversible on experimental time scales. Examples are negligible desorption, slow surface diffusion, or surface-induced conformational or orientational changes. When irreversible aspects are present, the state of an adsorbed layer at a given time depends on its history, implying that the kinetics of the adsorption process strongly influence the saturation or steady state of the adsorbed layer(s) (1). Thus, while important for all physical or chemical processes for predicting time evolution, kinetic models are especially important for protein adsorption.

It is frequently observed experimentally that protein molecules undergo, following adsorption, a transition in conformation and/or orientation (2–18). This transition usually leads to (i) a larger contact region, thus decreasing the probability that incoming proteins land on an unoccupied surface, and (ii) a stronger surface-binding, thus decreasing the rate of desorption. The transition tends to be disfavored when the surface is crowded due to steric blocking by neighboring proteins.

Clearly, the presence of a transition affects the kinetics of the adsorption process and vice versa. A truly universal adsorption model should incorporate the possibility of a post-adsorption transition, should account for the above experimental observations, and should predict, in addition to the total adsorbate surface density, the fraction of molecules in an altered state.

Recently, Van Tassel et al. presented an adsorption model in which proteins are considered to be disks that adsorb sequentially, randomly, and without overlap onto a surface (19–22). Once adsorbed, two competing events take place. The protein may desorb, or it may spread symmetrically and instantaneously to a disk of larger diameter. Both of these occur at given rates. Spreading can only occur if space allows and represents a post-adsorption transition in conformation or orientation. The key assumptions of this model are that (i) proteins interact laterally through a hard-core potential, (ii) only a single altered state is possible, (iii) the surface projections of both spread and unspread states are circular, and (iv) surface diffusion is negligible. A depiction of the model system is given in Fig. 1.

The kinetic equations for this process are

\[
\frac{\partial \rho_a}{\partial t} = k_c \Phi_a(t; \Sigma, K_a, K_d)
\]

\[
- k_d \rho_a \Psi_{ab}(t; \Sigma, K_a, K_d) - k_d \rho_a \]  

\[
\frac{\partial \rho_b}{\partial t} = k_a \rho_a \Psi_{ab}(t; \Sigma, K_a, K_d),
\]

where \(\rho_a\) is the density of proteins in the unspread state, \(\rho_b\) is the density of proteins in the spread state, \(k_s\) is the intrinsic adsorption rate, \(c\) is the bulk protein concentration, \(k_s\) is the spreading rate, \(k_d\) is the desorption rate, and \(\Phi_a\) and \(\Psi_{ab}\) are, respectively, the probability that an incoming protein finds space available for adsorption to the surface and the probability that an adsorbed protein has sufficient space to spread. These functions depend on time and the reduced variables \(\Sigma = R_p/R_a\) (the ratio of protein radii after and before the spread), \(K_s = k_s/k_c \pi R_a^2\), and \(K_d = k_d/k_c \pi R_a^2\). (We consider only the simplest case of a constant flux to the surface. In Section IV, we discuss more realistic and/or more complicated cases.)
Van Tassel et al. were able to derive approximate analytical expressions for $\Phi_a$ and $\Psi_{ab}$ only for $K_d = 0$ (20, 22). In this purely irreversible case, a density expansion approach coupled with asymptotic scaling yielded an accurate, albeit mathematically cumbersome, solution. For nonzero $K_d$, only the asymptotic kinetic scaling could be determined analytically, and computer simulation was required to evaluate the short to intermediate time behavior of this model (21).

The approach that succeeded when $K_d = 0$ was inspired by methods used to treat the purely irreversible adsorption of disks (the random sequential adsorption model (25)). Such an approach is unlikely to succeed here due to the presence of a relaxation mechanism (desorption). Since desorption allows the proteins in the $\alpha$ state to approach a translational equilibrium, a reasonable approximation would be to consider all the proteins on the surface to be in a state of translational equilibrium, a reasonable approximation would be to consider all the proteins (or, more generally, “particles”) on the surface are at all times in an equilibrium distribution, then these functions may be approximated using the SPT as follows. One begins by relating the reversible work required to create a cavity of radius $R$ that is free from any part of any particle, $W(R)$, to the probability of finding such a cavity in the equilibrated system, $P_0(R)$ (23, 24),

$$\beta W(R) = -\ln P_0(R),$$

where $\beta$ is the reciprocal of the Boltzmann constant times the absolute temperature. For a 2D binary mixture of circular particles of diameters $R_a$ and $R_b$ and densities $\rho_a$ and $\rho_b$, interacting via a hard-core repulsive potential, the value of $P_0$ is known exactly for $R \leq 0$ since such a cavity can be blocked by at most one particle. (A cavity of negative radius may be thought of as a point approachable by a particle center up to a threshold distance less than the particle radius.) For nonnegative cavities, a power series expansion is used:

$$P_0(R) = \ln[1 - \pi(R + R_a)^2 \rho_a - \pi(R + R_b)^2 \rho_b] \quad R \leq 0$$

$$= \beta W(0) + \beta W'(0) + \beta P \pi R^2$$

$$R > 0.$$  

In Eq. [4], $P$ is the pressure of the 2D binary disk mixture.

To obtain $W$ to second order in $R$, $P$ must be determined. This is done by noting that the excess chemical potentials of species $\alpha$ and $\beta$ are just the reversible work required to create cavities of size $R_a$ and $R_b$, respectively: $\mu_{\alpha}^e = \mu_a - \mu_{a}^0 = W(R_a)$ and $\mu_{\beta}^e = \mu_b - \mu_{b}^0 = W(R_b)$ ($\mu_i^0$ is the chemical potential of an ideal gas of species $i$). By differentiating $\mu_{\alpha}^e$ and $\mu_{\beta}^e$ with respect to $\rho_a$, employing the Gibbs–Duhem equation in the form

$$\frac{\partial \beta P^{ex}}{\partial \rho_a} = \frac{\partial \beta \mu_{\alpha}^{ex}}{\partial \rho_a} + \frac{\partial \beta \mu_{\beta}^{ex}}{\partial \rho_a},$$

solving for the derivative of the excess pressure ($P^{ex} = P - P^0$), and integrating this derivative with respect to $\rho_a$, one obtains

$$\beta P = \frac{\rho_a + \rho_b - \pi(R_b - R_a) \rho_a \rho_b}{1 - \pi R_a^2 \rho_a - \pi R_b^2 \rho_b},$$

as originally reported (24). Inserting Eq. [6] into Eq. [4], one obtains

$$\beta W(R) = \ln[1 - \pi R_a^2 \rho_a - \pi R_b^2 \rho_b]$$

$$+ \frac{2 \pi R_b \rho_a + R_b \rho_b}{1 - \pi R_a^2 \rho_a - \pi R_b^2 \rho_b}$$

$$+ \frac{\pi R^2 [\rho_a + \rho_b - \pi(R_b - R_a)^2 \rho_a \rho_b]}{1 - \pi R_a^2 \rho_a - \pi R_b^2 \rho_b}.$$
The function $\Phi_\alpha$ is defined as the probability of finding a cavity of radius $R_a$; i.e., $\Phi_\alpha = P_\alpha(R_a) = \exp(-W(R_a))$. The function $\Psi_{\alpha\beta}$ is determined as the conditional probability of finding a cavity of radius $R_\beta$ given that a particle of diameter $R_a$ exists in its center. Since, according to the SPT, a particle exerts the same influence on a fluid as does a similarly sized cavity (23, 24), we have $\Psi_{\alpha\beta} = P_{\alpha\beta}(R_\beta)/P_\alpha(R_a)$. Applying these definitions to Eq. [7] and defining dimensionless densities $\rho_i^* = \rho_i \pi R_i^2$, $i = \alpha$ or $\beta$, we finally obtain

$$\Phi_\alpha = (1 - \theta) \exp \left[ -\frac{2(\rho_\alpha + \Sigma \rho_\beta)}{1 - \theta} \right]$$

$$\Psi_{\alpha\beta} = \exp \left[ -\frac{2(\Sigma - 1)(\rho_\alpha + \Sigma \rho_\beta)}{1 - \theta} \right]$$

$$- \frac{(\Sigma - 1)[\rho_\alpha + \rho_\beta + (\Sigma - 1)^2 \rho_\alpha \rho_\beta]}{(1 - \theta)^2},$$

where, for simplicity, we drop the asterisk notation from the dimensionless densities and define $\theta = \rho_\alpha + \Sigma^2 \rho_\beta$, where $\Sigma = R_\beta/R_a$.

III. RESULTS

In Figs. 2 and 3, we show kinetic curves for the total and partial densities of the spreading disk model calculated (i) by integrating Eqs. [1] and [2] using the SPT-approximated probability functions given in Eqs. [8] and [9] and (ii) by computer simulation (for simulation details, see Ref. (21)). We note that for several sets of parameters, the agreement between theory and simulation is excellent for the total density and quite good for the partial densities. When the desorption rate is low ($K_\alpha = 0.01$), the agreement, although still acceptable, worsens somewhat. This is understandable since in this case, the system is expected to be far from the equilibrium approximation of the SPT.

When $K_\alpha = 0$, the adsorption is purely irreversible and density expansion theory (DET) becomes a valid means to approximate the adsorption and spreading probability functions (20). In DET, the probability functions are expressed as products or ratios of polynomials that reduce to the known power series expansion for short times and to the proper scaling behavior for long times (25, 30). In Fig. 4, we compare the SPT and DET approaches to simulation for two sets of parameters. We find that for a slower spreading rate, the former provides a better prediction, and for a faster spreading rate, the latter is superior. The DET tends to break down at high density, so it is understandably unable to predict a maximum in $\rho_\alpha$ occurring at a relatively high density as is the case when $K_\alpha$ is small. On the other hand, the density expansion approach is markedly superior to the SPT when $K_\alpha$ is large. In particular, we note that the SPT greatly underpredicts $\rho_\alpha$; this is likely due to the fact that many pairs of $\alpha$-proteins permanently block one another from spreading in purely irreversible adsorption, a feature captured by the DET but not by the SPT.

It is interesting to compare our model, in which proteins adsorb in one state and then (possibly) change to another, to a previously described model where proteins may adsorb directly into one of two states (28, 29, 31, 32). Specifically, we wish to compare the spreading disk model to a model of adsorption of a binary mixture of reversible $\alpha$- and irreversible $\beta$-proteins (this model has been proposed previously by Kurrat et al. (31, 32)). In the latter, we take the adsorption rate of $\alpha$- and $\beta$-proteins as $1/(1 + K_\alpha)$ and $K_\alpha/(1 + K_\alpha)$, respectively. We use the SPT to evaluate both of these models and show the resulting kinetic curves in Fig. 5. One clear distinction is at short times, where $\rho_\alpha \sim t$ and $\rho_\beta \sim t^2$ in the spreading disk model while both densities are linear in time for the mixture.
model. This is most pronounced when $K_s$ is moderate or large and may lead to substantially differing kinetic curves. In other cases, the two models yield kinetic curves similar enough that comparison with experiment would be unlikely to distinguish between these two adsorption mechanisms.

IV. DISCUSSION

In this article, we present a scaled particle theory (SPT) approach for determining the probability functions needed to model protein adsorption as the surface-filling of spreading disks. This approach is promising for modeling real experimental systems due to the tractability of the mathematical expressions and the generally good agreement with computer simulation. Any disagreement with simulation results from two approximations. The first of these is the assumption that the proteins on the surface are always in a state of 2D thermodynamic equilibrium. Since sequential placement will not by itself result in an equilibrium configuration (33), by employing the SPT, we are implicitly assuming that the proteins relax to an equilibrium configuration rapidly between successive adsorption, desorption, or spreading events. Experimentally, this is most likely to be true when the proteins diffuse rapidly on the surface and when conditions are such that lateral interactions are largely screened. The second approximation rests with the SPT itself. Like all available liquid theories, it provides only an approximate description of the equilibrium state in dimensions greater than one.

We report good agreement with simulation throughout most of the parameter space. One case in which agreement is somewhat poor occurs when $\rho_a$ displays a maximum at short times. In this case, a small but appreciable saturation $\alpha$-density results due to the irreversible placement of pairs of $\alpha$-proteins of separation too small for spreading to occur. The SPT cannot capture this feature since a neighboring pair would not be

![Figure 4](image4.png)

**FIG. 4.** The dimensionless adsorbed density versus dimensionless time for the spreading disk model as determined by simulation (21), by the SPT, and by a purely irreversible density expansion theory (DET) (20, 22), for $\Sigma = 1.05$, $K_d = 0$ and (a) $K_s = 1$, $K_s = 10$. The SPT approach is generally superior when $K_s$ is of order 1 or less.
“locked in” to such close proximity in an equilibrated system. Fortunately, the density expansion theory presented earlier (2, 4) provides an accurate prediction in this case. We contend that, together, these two theories allow accurate predictions to be made over most of the parameter space.

An alternative to the spreading disk model is one where \(a\)- and \(b\)-proteins adsorb directly to the surface (the latter irreversibly) (31, 32). Both of these models can predict partially reversible adsorption and nonmonotonic \(a\)- or total densities with time. The basic difference is the mechanism for placement of a \(b\)-protein, direct as in the mixture model or indirect via an \(a\)-intermediate in the spreading model. This results in the following initial kinetic behavior: at short times, in the spreading model, one finds \(\rho_a \sim t, \rho_b \sim t^2\) (the latter reflects the two-step process of \(b\)-protein placement) while in the mixture model, both densities increase linearly with time. This is evident in Fig. 5. The different modes of \(b\)-protein placement are likely to lead to larger differences when the surface is crowded. In this situation, which arises when \(K_d\) is small, adsorption of a large \(b\)-protein directly on the surface is less likely to occur than is adsorption and subsequent spreading of a smaller \(a\)-protein. Although it seems more likely that the path to a surface-altered protein would likely pass through an intermediate adsorbed state, the mixture model may be useful in predicting certain two-state experimental adsorption situations. In addition to the models discussed here, we point out that the SPT may also be applied to more complicated adsorption models, such as those with multiple transitions and/or nondisk shaped proteins.

In this work, we develop a theoretical approximation to a simple yet reasonable model of the protein adsorption process. The accuracy of the theory is readily verified by comparison with computer simulation of the model system. One can and should also question the ability of the model itself to reflect reality. This can only be tested by comparison with experiment. An important feature to consider when making such a comparison is the transport of the protein from the bulk solution to the surface. This involves convection, diffusion, and interactions with the surface and previously adsorbed proteins. Several other authors have considered the details of the interfacial transport step (34 – 41). In order to facilitate comparison with other models and simulation, and since our contribution here deals with aspects of adsorption following arrival at the surface, we present governing equations only for the simple case of a constant surface flux \(k_a\). (We further note that such a presentation is quite standard in the theoretical/modeling literature.) To apply our model to a real system, one must consider the dependence of the transport coefficient \(k_a\) on the flow conditions and perhaps on time. (For example, in adsorption from a still liquid or from a flowing liquid at short times, \(k_a\) will have an explicit time dependence. For a flow system at steady state in the diffusion limited regime, \(k_a\) may depend on the surface density, and thus indirectly on time.) A meaningful comparison with experiment of course requires that a transport mechanism be coupled with the adsorption model through careful choice of \(k_a\).

V. SUMMARY

We use the scaled particle theory to approximate the adsorption and spreading probability functions needed to solve the rate equations for a spreading disk protein adsorption model. Although derived as an approximate theory for an equilibrium system, the SPT is shown here to accurately predict results from computer simulation over most regions of parameter space. The hope is that the SPT approximated spreading disk model will be useful in predicting the adsorption kinetics of proteins and other macromolecules where surface-induced transitions occur.
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