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Time Dependent Desorption: A Memory Function Approach

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Abstract. A formalism for the adsorption kinetics of systems where the desorption rate is a function of the residence time of the adsorbed particle is presented. The adsorbed density at time t is expressed simply as a convolution of a memory kernel, $Q(t)$, and the available surface function, $\phi(t)$. For completely irreversible adsorption, $Q(t) = 1$, while for a system which approaches an equilibrium state, Q tends to zero at sufficiently large times. When the desorption rate, k_d, is constant, $Q(t) = \exp(-k_d t)$. Two models for the memory kernel are considered. In the first, the molecule is assumed to interact with the surface via two ligands which bind and debind at rates λ and μ respectively. In the second model, the adsorption is assumed to be partially reversible: molecules transform to a permanently bound state at a rate λ and desorb at a rate μ. In both models, the adsorption kinetics and memory kernels are found analytically. Strategies for determining the memory function from experimental data are discussed.

Keywords: protein adsorption, desorption, memory function

1. Introduction

The adsorption of proteins, and macromolecules in general, is a complex process, yet advances in the molecular level understanding of the adsorption mechanism are potentially of great significance for a number of applications ranging from biocompatibility to separations (Andrade and Hlady, 1986). An accurate description of the kinetics is essential in e.g., chromatography where non-equilibrium effects are ubiquitous. In attempting to develop models for the adsorption process, it is useful to consider up to five elementary steps: (i) transport of the molecule to the adsorbing surface, (ii) an attachment step, (iii) rearrangement of the conformation of the adsorbed molecule in response to the change in microenvironment, (iv) a detachment step, and (v) diffusion away from the surface. Although some of these elementary process are well understood, particularly those involving particle transport (Adamczyk et al., 1994; Rajagopalan and Kim, 1977; Matijevic et al., 1987), there exists no entirely satisfactory, comprehensive, theory. The situation is further exacerbated by the tendency for the adsorption to be partially or completely irreversible. Experimental kinetic data are frequently analyzed with the Langmuir equation:

$$\frac{d\rho}{dt} = k_a c(\rho_{\max} - \rho) - k_d \rho \tag{1}$$

where ρ is the surface density of the adsorbed species, c is the concentration of the solute immediately above the adsorbing surface, $\rho_{\max}$ is the capacity and k_a and k_d are the adsorption and desorption constants, respectively. One problem with the Langmuir equation, particularly when applied to the adsorption of large molecules, is that it does not accurately represent the surface exclusion effects of the adsorbed layer, which result in a more rapidly diminishing rate of adsorption than possible according to (1). To overcome this difficulty, a generalized Langmuir equation has been proposed (Schaaf and Talbot, 1989; Jin et al., 1994),

$$\frac{d\rho}{dt} = k_a c\phi(\rho) - k_d \rho \tag{2}$$

where $\phi(\rho)$ is the available surface function with the property that $\phi(0) = 1$. Physically, ϕ represents

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the probability that a molecule arriving at the interface covered with particles at an average density ρ is not obstructed by the preadsorbed particles. Various expressions for ϕ have been developed for irreversible adsorption, $k_d = 0$, for a number of systems including spherical and non-spherical particles and mixtures. If desorption is present, the system may evolve to an equilibrium state in which the available surface function is simply related to the chemical potential of the adsorbed species. As an example of the success of this approach, kinetic expressions based on the generalized Langmuir equations have been shown to provide a better description of the slow approach to saturation for colloid (Adamczyk et al., 1994) and protein (Jin et al., 1993; Ramsden, 1993) adsorption than the simple Langmuir equation itself.

It is the purpose of this article to consider in more detail the desorption term, $k_d\rho$, of the generalized Langmuir equation. The motivation for this study is that a number of experimental studies have shown that, for the adsorption of some proteins, the desorption rate is a function of the residence time of the adsorbed molecule (Soderquist and Walton, 1980; Beissinger and Leonard, 1980; Mura-Galelli et al., 1991). This behavior is thought to result from conformational changes that are driven by hydrophobic interactions. By unfolding, a protein may optimize its interaction with the surface and, in so doing, it becomes more strongly bound to the surface. This behavior is not universal, however: proteins which do not undergo any significant conformational change at an interface may not show a time-dependent k_d. The effect may also be present whenever multisite binding between the solute and the interface is possible.

The use of (1) or (2) with a constant k_d severely limits the mechanism of desorption. More specifically, it implies that the adsorbed molecules desorb in a completely random fashion and independently of the residence time on the surface. This picture is certain to be invalid for the cases discussed above where a solute becomes more strongly bound to the surface with increasing residence time and, consequently, its desorption probability decreases.

2. Theory

Consider an adsorption process on an initially empty surface. In an infinitessimal time interval dt_1 at time t_1, a number $k_a c\phi(t_1)dt_1$ solutes are adsorbed on the surface per unit area. We now introduce the memory kernel, $Q(t, t_1)$, to denote the fraction of molecules adsorbed at t_1 that remain adsorbed at t. Clearly, $Q(t_1, t_1) = 1$. If we assume that the desorption probability is not affected by the environment of the particle, i.e., it is independent of the surface density, then the memory function depends only on the time difference, so that we may use simply $Q(t - t_1)$. Now the total density of adsorbed particles at time t is the integral

$$\rho(t) = k_a c \int_0^t \phi(t_1) Q(t - t_1)\, dt_1 \tag{3}$$

We now see what this equation implies for the form of Q when the desorption rate, k_d, is constant. Considering (2) as a linear, first order ordinary differential equation, and solving for $\rho(t)$ yields

$$\rho(t) = k_a c \int_0^t \phi(t_1) e^{-k_d(t-t_1)}\, dt_1 \tag{4}$$

from which it is clear that

$$Q(t) = e^{-k_d t} \tag{5}$$

which is the cumulative probability distribution of a Poisson process. For irreversible adsorption, $k_d = 0$, by definition, and all adsorbed molecules remain on the surface and $Q = 1$. A necessary condition for the system to reach equilibrium is $\lim_{t\to\infty} Q(t) = 0$. The isotherm equation is simply

$$\rho_{\text{eq}} = k_a c \phi_{\text{eq}} \int_0^\infty Q(t)\, dt \tag{6}$$

since there is always a finite time for which $\phi(t)$ approaches a constant value, ϕ_{eq}. One may use (3) to compute an effective time-dependent desorption rate. In general, the expression is

$$k_d(t) = -\frac{\int_0^t \phi(t_1) Q'(t - t_1)\, dt_1}{\int_0^t \phi(t_1) Q(t - t_1)\, dt_1} \tag{7}$$

where $Q'(t) = dQ(t)/dt$. It is also interesting to consider the distribution of residence times of the adsorbed molecules. Let $f(\tau; t)d\tau$ denote the fraction of the latter at time t that have been on the surface for a time τ. Then

$$f(\tau; t) = \frac{\phi(t - \tau) Q(\tau)}{\int_0^t \phi(t_1) Q(t - t_1)\, dt_1} \tag{8}$$

If the system reaches equilibrium

$$f_{eq}(\tau) = \frac{Q(\tau)}{\int_0^\infty Q(t)\,dt} \tag{9}$$

These equations may be used to derive various averages of the residence time.

It is straightforward to generalize the approach to encompass a number of common experimental procedures. For example, if the solution is replaced with a buffer solution ($c = 0$) at time t_0, the flux of particles to the surface ceases at t_0 and the density at time t ($t > t_0$) is given by

$$\rho(t) = k_a c \int_0^{t_0} \phi(t_1) Q(t - t_1)\,dt_1 \tag{10}$$

A special case of this equation is when the system is initially in equilibrium at time $t = 0$. The amount which has desorbed at time t is

$$\Delta\rho(t) = \rho_{eq} - \rho(t) = k_a c \phi_{eq} \int_0^t Q(t)\,dt \tag{11}$$

3. Model I: Reversible Adsorption via Two Ligands

We next consider a simple model for a solute which has two ligands which may bind to the surface. Each ligand exists in one of two states: unbound or bound. An unbound ligand binds to the surface at a rate λ, while a bound ligand debinds at a rate μ. We make the usual assumptions in a Poisson process: namely that the probability for e.g., a unbound ligand to bind to the surface in a time interval Δt is $\lambda\Delta t$ and the probability for two events in the same time interval is $O((\Delta t)^2)$. A molecule may thus be in one of three states which we label 0, 1 or 2 according to the number of bound ligands. A molecule is considered to be adsorbed if at least one ligand is bound to the surface.

Desorption is then only possible from state 1. Let $\rho_1(t)$ and $\rho_2(t)$ denote the surface density of solutes which are bound via one or two ligands respectively. The time evolution of these densities is governed by the following equations:

$$\begin{aligned} \frac{d\rho_1}{dt} &= k_a c\phi(t) - (\lambda + \mu)\rho_1 + 2\mu\rho_2 \\ \frac{d\rho_2}{dt} &= -2\mu\rho_2 + \lambda\rho_1 \end{aligned} \tag{12}$$

with initial conditions $\rho_1(t) = \rho_2(t) = 0$. The factor 2 accounts for the fact that either one of the two bound ligands of a molecule in state 2 may desorb, leaving the solute in state 1. To simplify the analysis, we will assume here that there are no surface exclusion effects—valid only at very low surface coverages. In this case, $\phi(t) = 1$ and the equations have the following solution:

$$\rho_1(t^*) = \frac{k_a c}{\mu}\left[1 - e^{-\frac{3+\lambda^*}{2}t^*}\left((1+\lambda^*)\delta^{-1}\sinh\left(\frac{\delta}{2}t^*\right) + \cosh\left(\frac{\delta}{2}t^*\right)\right)\right] \tag{13}$$

$$\rho_2(t^*) = \frac{k_a c\lambda^*}{2\mu}\left[1 - e^{-\frac{3+\lambda^*}{2}t^*}\left((3+\lambda^*)\delta^{-1}\sinh\left(\frac{\delta}{2}t^*\right) + \cosh\left(\frac{\delta}{2}t^*\right)\right)\right] \tag{14}$$

where we have introduced the reduced time, $t^* = \mu t$, $\lambda^* = \lambda/\mu$, and $\delta = \sqrt{(1 + 6\lambda^* + \lambda^{*2})}$. The density of adsorbed particles is $\rho = \rho_1(t) + \rho_2(t)$, and the isotherm is given by

$$\rho_{eq} = \frac{k_a c}{\mu}\left(1 + \frac{\lambda}{2\mu}\right) \tag{15}$$

For $\phi = 1$, we easily find from (3) that $d\rho/dt = k_a c Q(t)$ and from (12) that $Q(t) = 1 - \mu\rho_1(t)/k_a c$. Figure 2 illustrates the time dependent densities for two sets of the adsorption parameters. These are chosen so that the equilibrium amount of the total density is the same. As expected, a smaller value of λ results in lower occupancy of state 2 at all times. Figure 3 shows the memory kernel for a number of different values of λ. While the initial slope is the same in all cases (-1),

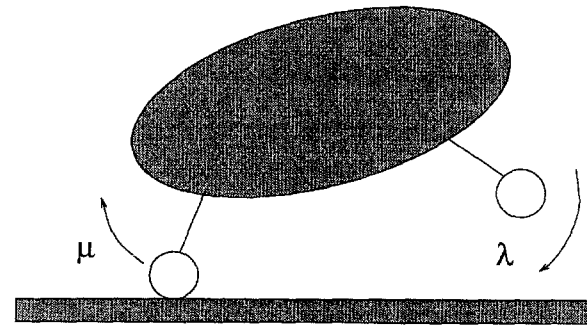


Figure 1. Schematic illustration of the two-site binding model. The molecule is shown in state 1 with one bound site (1) which desorbs at a rate μ, while the unbound site (2) binds at a rate λ. A molecule desorbs if both sites are unbound.

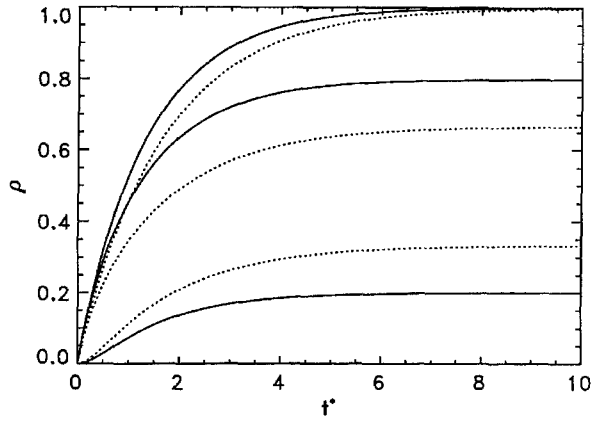


Figure 2. Density of the adsorbed molecules in states 1 and 2 and their sum as a function of reduced time for the two site binding model. Solid lines: $k_a c/\mu = 4/5$, $\lambda^* = 1/2$; dotted lines: $k_a c/\mu = 2/3$, $\lambda^* = 1$.

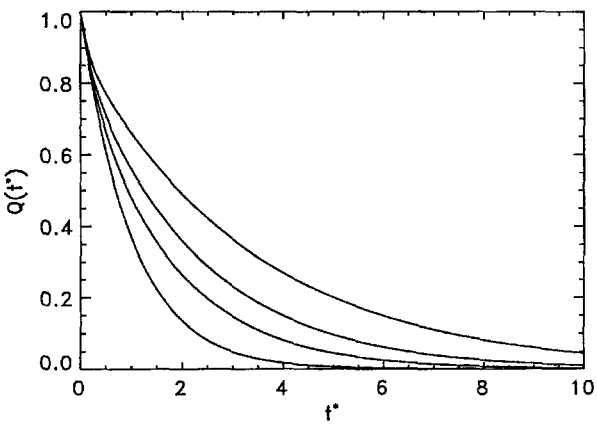


Figure 3. The memory kernel, $Q(t)$, versus the reduced time t^* for a number of values of the relative binding rate $\lambda^* = 0, 1, 2, 4$, bottom-to-top, for the two site binding model.

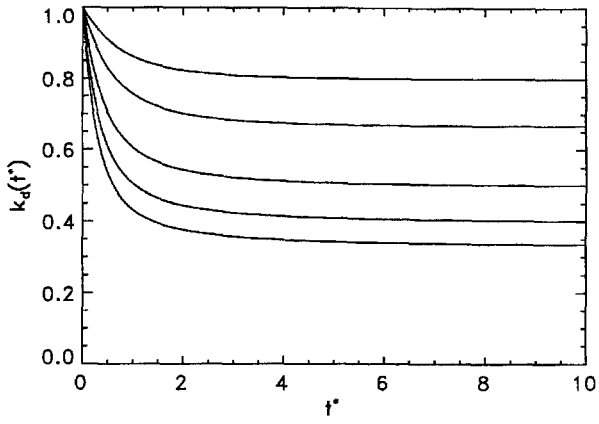


Figure 4. The effective desorption rate of the two site binding model as a function of reduced time for different values of the binding rate: $\lambda = 0, 0.5, 1, 2, 4$ (top-to-bottom). The rate approaches an asymptotic value of $2/(2+\lambda)$.

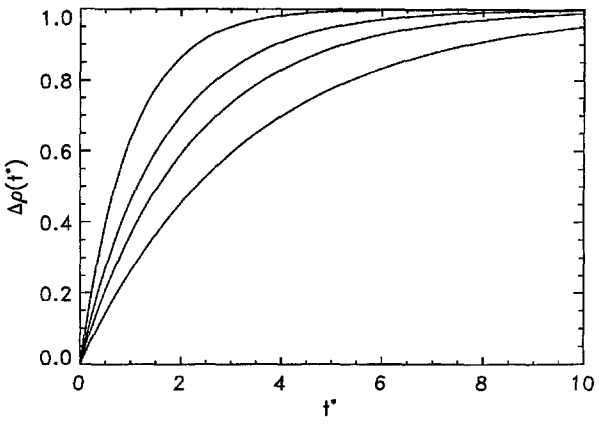


Figure 5. Amount desorbed as a function of reduced time for two site binding model. Top to bottom: ($\lambda^* = 0, k_a c/\mu = 1$), (1, 2/3), (2, 1/2), (4, 1/3). The values of the parameters $k_a c/\mu$ and λ^* were chosen to give the same initial (equilibrium) density, $\rho_{eq} = 1$.

increasing λ increases the probability that a molecule remains on the surface.

The effective time-dependent desorption rate for this model may be computed using (7). The resulting expression is cumbersome and not presented here. However, some numerical results are shown in Fig. 4. For the range of λ considered, the desorption rate constant decreases to an asymptotic value of $k_d(\infty) = 2/(2+\lambda^*)$ after a reduced time of $\lambda \approx 4$. Finally, in Fig. 5 some results for the desorption experiment are presented. At $t = 0$ the adsorbed phase is in equilibrium with the bulk, which is then replaced with a buffer solution. The change in density is calculated using (11).

A number of generalizations and extensions of the model are possible. For m ligands or states one may show that the isotherm equation is

$$\rho_{eq} = \frac{k_a c}{\lambda m}\left[\left(1+\frac{\lambda}{\mu}\right)^m - 1\right] \tag{16}$$

As expected, increasing m greatly increases the adsorbed amount. Unfortunately, it does not appear possible to obtain an analytic solution for the kinetics in the general case. However, one expects that with increasing m larger deviations from the ideal (no memory) case will occur and that the rate of relaxation

to the plateau value in the time-dependent k_d will decrease.

4. Model II: Partial Reversibility

In many experiments, only a fraction of the adsorbed protein may desorb (Ramsden, 1993). We model this as follows. A molecule initially adsorbs in state 1 whereupon it desorbs at a rate μ or becomes irreversibly bound at a rate λ. The kinetic equations are

$$\frac{d\rho_1}{dt} = k_a c\phi(\rho_1, \rho_2) - (\mu + \lambda)\rho_1$$
$$\frac{d\rho_2}{dt} = \lambda\rho_1 \tag{17}$$

which yields the following solution in the case of a Langmuirian available surface function, $\phi(\rho_1, \rho_2) = 1 - \rho_1 - \rho_2$:

$$\rho_1(t) = \epsilon^{-1} \exp\left(-\frac{1+\lambda+\mu}{2}t\right) \sinh(\epsilon t) \tag{18}$$

and

$$\rho_2(t) = 1 - \epsilon^{-1} \exp\left(-\frac{1+\lambda+\mu}{2}t\right) \times \left(\epsilon \cosh(\epsilon t) + \frac{1+\lambda+\mu}{2} \sinh(\epsilon t)\right) \tag{19}$$

where $\epsilon^2 = (-4\lambda + (1+\lambda+\mu)^2)^2/4$ and we have expressed time in units of $k_a c$. The memory kernel is most easily found by working with the Laplace transform of (3):

$$\hat{\rho}(s) = k_a c \hat{\phi}(s) \hat{Q}(s) \tag{20}$$

and has the following form:

$$Q(t) = \frac{1}{\mu+\lambda}(\lambda + \mu e^{-(\mu+\lambda)t}) \tag{21}$$

As expected, the memory function does not approach zero at long times, but rather the constant value $\lambda/(\mu+\lambda)$. Figure 6 shows some examples of the kinetic behavior of model II, while Figure 7 shows the time-dependent desorption rate for this model.

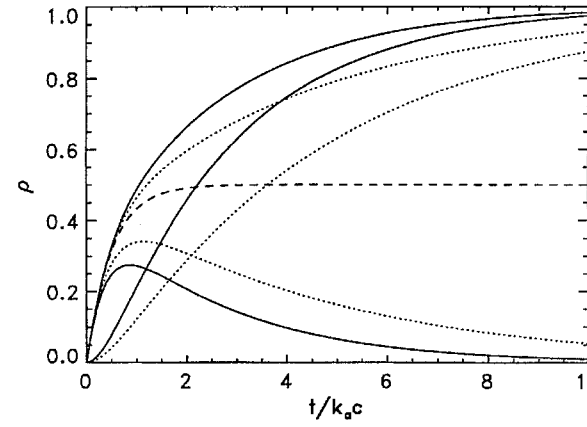
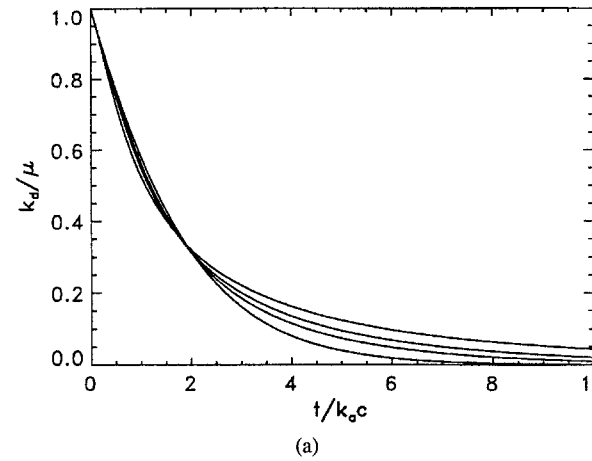


Figure 6. Adsorbed densities of model II. Solid lines: $\lambda = \mu = 1$. Dotted lines $\lambda = 0.5$, $\mu = 1$. Dashed line: the fully reversible case, $\lambda = 0$, $\mu = 1$. In the first two sets, ρ_2 has a local maximum and the total density is the sum, $\rho = \rho_1 + \rho_2$.



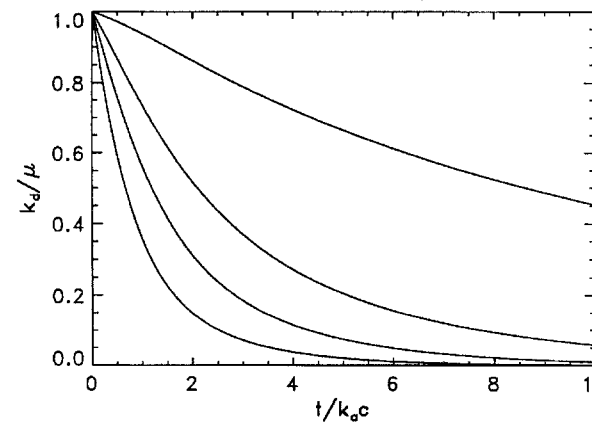


Figure 7. Time dependent desorption rate for model II. (a) λ = constant = 1, top-to-bottom, right side $\mu = 5, 2, 1, 0.1$ (b) μ = constant = 1, top-to-bottom $\lambda = 0.1, 0.5, 1, 2$.

5. Discussion

We have presented a new approach for the analysis of time-dependent desorption which is a common phenomenon in protein adsorption. For purely irreversible adsorption, all adsorbed molecules remain on the surface and $Q(t) = 1$. For partial desorption, $Q(t)$ decreases from unity to a finite value. The experimental determination of $Q(t)$ may provide some insight into the nature of the time-dependent solute-surface binding.

The following experimental methods might be used in the determination of $Q(t)$. If the surface exclusion effects are negligible, which would be the case at short times and/or low surface site densities, then the rate of adsorption is directly related to $Q(t)$:

$$\frac{d\rho}{dt} = k_a c Q(t) \tag{22}$$

Alternatively, if these conditions do not apply one could perform a desorption experiment. The system would be allowed to reach equilibrium at a bulk concentration c, after which the supernatant solution is replaced with a buffer solution. The rate of change of the desorbed amount may be found simply from (11). With $Q(t)$ in hand, the available surface function $\phi(t)$ may then be found from an adsorption experiment. For this calculation, it would be most convenient to work with the Laplace transforms, (20).

The approach also raises a number of interesting theoretical issues. It is clear that if the system is to reach equilibrium, $Q(t)$ must approach zero at long times. However, is this a *sufficient* condition? That is, is the behavior $\lim_{t\to\infty} Q(t) = 0$ sufficient to guarantee that the system evolves to an equilibrium state? Can $Q(t)$ approach zero according to a power law? We have not addressed the development of theories for $\phi(t)$, which may be very different from that of the simple RSA model, even at low coverages.

It is also possible to interpret the states in an alternative way. State "0" denotes a desorbed molecule, while states "1" and "2" denote adsorbed molecules, with the latter corresponding to a more strongly bound molecule than the former. Recent work has investigated the kinetics of a purely irreversible model for particle denaturation upon adsorption in which an initially adsorbed particle spreads to a larger diameter if space allows (Van Tassel et al., 1994). It would be of interest to extend this model to allow for desorption from one or both states.

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