Late stage of the formation of a protein corona around nanoparticles in biofluids

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In biofluids containing various proteins, nanoparticles rapidly come to be surrounded by a nanometer-thick protein layer referred to as a protein corona. The late stage of this process occurs via replacement of proteins already bound to a nanoparticle by new ones. In the available kinetic models, this process is considered to include independent acts of protein detachment and attachment. It can, however, occur also at the level of protein pairs via exchange, i.e., concerted replacement of an attached protein by a newly arrived one. I argue that the exchange channel can be more important than the conventional one. To illustrate the likely specifics of the exchange channel, I present a kinetic model focused exclusively on this channel and based on the Evans-Polanyi-type relation between the activation energies of the protein-exchange steps and the protein binding energies. The corresponding kinetics were calculated for three qualitatively different distributions of proteins in solution over binding energy (with a maximum or monotonously decreasing or increasing, respectively) and are found to be similar, with relatively rapid replacement of weakly bound proteins and slow redistribution of strongly bound proteins. The ratio of the timescales characterizing the evolution of weakly and strongly bound proteins is found to depend on the type of the binding-energy distribution.

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I. INTRODUCTION

The formation of a nanometer-thick protein corona (PC) around nanoparticles (NPs) in biofluids is of appreciable intrinsic interest and also important in the context of numerous potential applications of NPs (reviewed in Refs. [1–5]). Mechanistically, due to the diversity of proteins in biofluids, this process starts by adsorption of small proteins with the highest diffusion and attachment rates but eventually they are replaced by proteins with larger size and binding energy (Vroman effect). These steps can be accompanied by denaturation of adsorbed proteins. In the kinetic models of the PC formation [6–11] (reviewed in Ref. [5]), the whole PC-formation process is described by using the models implying the conventional mechanism including independent attachment of individual proteins to vacant sites and their detachment from occupied sites.

The timescales characterizing different stages of the PC formation depend on the type of NPs. In the context of basic studies, one of the most interesting case is NPs fabricated of SiO_2, because the protein adsorption at this material was widely explored by using macroscopic samples as well as NPs. Concerning NPs, I can mention three studies important in the present context. In particular, (i) Vilanova *et al.* [8] have explored adsorption of albumin (67 kDa), transferrin (80 kDa), and fibrinogen (340 kDa) on SiO_2 NPs with different orders of their administration and observed a memory effect in the final PC composition. It is of interest to notice that in the experiments with preadsorption of albumin and transferrin followed by adsorption of fibrinogen the former two proteins were replaced by the latter one on the timescale somewhat shorter or about 10 min (see, e.g., Fig. 4 in Ref. [8]). The corresponding kinetics were shown to be not described by the conventional Langmuirian equations but can be described by using the conventional model with the coverage-dependent rate constants for desorption. The values of these rate constants and the type of the coverage dependence were fitted. (ii) Frost *et al.* [12] have shown that albumin or immunoglobulin ($\sim$150 kDa) preadsorbed on SiO_2 NPs and then exposed to bovine serum is exchanged by other proteins on the timescale of 50 min. (iii) More globally, Tenzer *et al.* [13] (see also Ref. [14]) have found that the formation of PC on SiO_2 NPs in human plasma takes place on the comparable timescale ($\sim$1 h) and then PC is stable on the timescale at least up to 6 h. The obtained protein binding profiles determined after 1 h do not simply correspond to the relative protein concentrations in the plasma. Although albumin as the protein with highest concentration in the plasma was also the most abundant in PC, the second most abundant plasma protein, α-2-macroglobulin (800 kDa), was only the 13th in PC. In addition, the experiments have revealed that PC is enriched by specific lipoproteins as well as by proteins involved in coagulation and the complement pathway, whereas immunoglobulins and acute phase response proteins displayed lower affinity. For comparison, the timescale characterizing the whole PC-formation process at Au NPs in bovine serum is about one day, and albumin is the most abundant component [15].

Basically, the experiments like those outlined above (Refs. [12–15]) show that a few hours in serum can be sufficient in order to observe the key stages of the PC formation

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including the initial protein adsorption and their redistribution (Vroman effect) and reaching the stable state. One can of course debate whether this stable state corresponds to thermodynamically stable adsorption-desorption equilibrium or to a state with irreversible adsorption at the maximal timescale of interest. Anyway, however, the transition to the observed stable state includes the Vroman effect for various protein species. This aspect of the PC formation is not trivial because numerous experiments performed with individual protein species at macroscopic samples indicate that after reaching appreciable coverage the protein adsorption is often practically (except a small fraction) irreversible (briefly reviewed in Refs. [16,17]; concerning albumin adsorption as an example, see, e.g., Refs. [18–20]; some other aspects of protein adsorption at macroscopic samples are also reviewed in Ref. [21]). Physically, this is indicative that the conventional adsorption mechanism, used often to explain the Vroman effect and including independent attachment and detachment of individual proteins, is not fully sufficient in order to interpret the late stage of the PC formation in biological media, because during this stage the dense protein layer forming PC is close to saturation and, if the attachment of appreciable fraction of proteins is irreversible, they will remain on the NP surface after adsorption and accordingly the PC composition will be close to that in solution while this is not the case.

One of the ways to handle the above-noted contradiction between the experiments and what is expected on the basis of the simplest conventional mechanism of adsorption is to take into account already mentioned denaturation of adsorbed proteins and to assume that their adsorption becomes irreversible on the timescale of observations only after denaturation and/or reorientation as often admitted in the context of protein adsorption at macroscopic samples (see, e.g., the discussion in Ref. [16] or the discussion concerning the schemes shown in Figs. 3 and 8 in Ref. [17]). If the protein uptake is appreciable, then the denaturation and/or reorientation can be slow and the protein detachment can still be operative. In fact, however, the denaturation typically does not appear to facilitate detachment of proteins remaining in the nearly native form and accordingly can hardly explain why the observed replacement of proteins and the formation of the apparently stable state of the overlayer is rapid.

An alternative explanation is to admit the exchange mechanism of protein adsorption, representing concerted replacement of an attached protein $\mathrm{P}_j^{\mathrm{at}}$ (of type j) by a protein $\mathrm{P}_i^{\mathrm{sol}}$ (of type i) from solution,

$$\mathrm{P}_i^{\mathrm{sol}} + \mathrm{P}_j^{\mathrm{at}} \rightarrow \mathrm{P}_j^{\mathrm{sol}} + \mathrm{P}_i^{\mathrm{at}}. \tag{1}$$

In the literature concerning protein adsorption at macroscopic samples, the denaturation of attached proteins has been widely studied and discussed (reviewed in Refs. [16,17,22]) partly because this process is possible even in the case of adsorption of proteins of one type and accordingly can be observed in numerous experiments focused on adsorption of specific proteins. In contrast, the protein exchange has attracted much less attention (briefly reviewed in Refs. [22,23]). At the generic level, the mathematical description of the latter adsorption channel is simple [24,25]. For example, the rate of adsorption of protein 1 accompanied by desorption of protein 2 is described as

$$w = k_{12}\theta_2 c_1, \tag{2}$$

where c_1 is the concentration of protein 1 in solution, θ_2 is the surface coverage corresponding to protein 2, and k_{12} is the properly normalized exchange rate constant.

The kinetic models of the PC formation at NPs, as already noticed, imply the conventional mechanism protein adsorption including independent attachment and detachment of single proteins without or with subsequent denaturation (Refs. [6–8] and [9], respectively). The inclusion of the exchange channel into these model can naturally be done by adding the terms similar to (2). A severe complicating factor here is that biofluids typically contain a large number of various proteins. For example, the human plasma contains ∼300 distinct proteins [26], and ∼20 of them are most abundant in PC at SiO_2 NPs [13]. In this case, theoretical calculations focused on general trends in the PC formation or attachment of specific proteins are far from straightforward. One of the reasons is that the information available in proteomics is now either insufficient or cannot be directly used to describe protein adsorption (this area is reviewed, e.g., in Ref. [27]). In biology and chemistry, this situation is not unique. Typical examples include complex genetic and neural networks (Refs. [28] and [29], respectively) and mutation of bacteria [30] and viruses [31] in biology and, e.g., catalytic cracking [32] in chemistry.

In chemistry, general trends in the kinetics of a series reactions with the same mechanism including a homologous step (with a similar transition state) can often be clarified taking into account that the activation energy of this step, E_a, is approximately proportional to its latent heat, ΔE, i.e.,

$$E_a = \alpha \Delta E + \beta, \tag{3}$$

where α and β are constants (reviewed in Ref. [33]). In the chemical literature, this relation is often associated with the seminal study by Evans and Polanyi [34] although it was based on or independently proposed in other works by Brønsted, Bell, and Semenov (reviewed, e.g., in Ref. [33]). In heterogeneous catalysis, the usefulness of the Evans-Polanyi relation was confirmed by Nørskov and coworkers (reviewed in Refs. [33,35]). In electrochemistry, a similar relation is widely used to describe the dependence of the reaction activation energies on the electrode potential where it is associated with the seminal studies by Butler and Volmer (reviewed in Ref. [36]).

Taking into account that the Evans-Polanyi relation is based on simple and physically sound ideas and applicable in various areas of chemical physics, I suggest herein to describe general trends of the late stage of the PC formation by employing a kinetic model with the key elements formulated by analogy with this relation.

II. MODEL

In general, the PC formation should be described by using the conventional channels of protein adsorption (including independent attachment and detachment of single proteins without or with subsequent denaturation) and the exchange cannel. The former channels are expected to dominate during

the initial stages of the kinetics and may be important at the late stage. The exchange cannel [steps (1)] can dominate at the late stage. Focusing on the latter stage, it makes sense to exclude the conventional channels in order to simplify the presentation and to articulate the role of the exchange cannel. In my analysis, this is done by neglecting vacant sites at the stage under consideration. This approximation is directly related but not fully identical to exclusion of the conventional channels because a vacant region sufficient for attachment of a protein can in principle be generated after a few acts of exchange of large proteins by smaller proteins. This effect is, however, expected to be minor and excluded here as well.

With the specification above, the late stage of the PC formation occurs via steps (1) and can be described in terms of the populations, n_i, of protein species forming PC around a NP. The rate of each exchange act can be represented by analogy with (2) replacing the protein coverage by n_i. This yields

$$\frac{dn_i}{dt} = \sum_{j\neq i}(k_{ij}c_i n_j - k_{ji}c_j n_i), \tag{4}$$

where c_i and c_j are concentrations of proteins i and j in solution. The corresponding exchange rate constants can be expressed in the Arrhenius form,

$$k_{ij} = \nu \exp\big(-E^a_{ij}/k_BT\big), \tag{5}$$

where E^a_{ij} is the activation energy and ν is the pre-exponential factor. E^a_{ij} are different for different protein species, whereas the pre-exponential factor is for simplicity considered to be the same because its variation is less important compared to that of E^a_{ij}.

In the framework of the conventional transition state theory, the activation energy for the exchange steps is given by

$$E^a_{ij} = E^*_{ij} - E^{\rm in}_{ij}, \tag{6}$$

where E^*_{ij} and $E^{\rm in}_{ij}$ are the energies of a pair of proteins, $\mathrm{P}^{\rm sol}_i$ and $\mathrm{P}^{\rm at}_j$, near the potential barrier (in the activated state) and before the exchange (in the initial state), respectively. To calculate E^*_{ij} and $E^{\rm in}_{ij}$, the energy of proteins in solution can be chosen as the baseline. With this specification, the introduced protein energies can be expressed via their binding energies, I_i (these energies are considered to be positive). In particular, the energy in the initial state is given by

$$E^{\rm in}_{ij} = -\langle I\rangle - \Delta I_j, \tag{7}$$

where $\langle I\rangle$ is the average binding energy of all the proteins and ΔI_j is the deviation from the average for protein j. In the activated state, proteins i and j are only partly bound to the NP surface, and accordingly their energy can be represented as

$$E^*_{ij} = \langle E^*\rangle - \alpha(\Delta I_i + \Delta I_j), \tag{8}$$

where $\langle E^*\rangle$ is the average value, and $\alpha < 1$ is a numerical coefficient introduced in the Evans-Polanyi spirit [Eq. (3)]. Then, substituting (7) and (8) into (6) yields

$$E^a_{ij} = \langle E_a\rangle - \alpha\Delta I_i + (1-\alpha)\Delta I_j, \tag{9}$$

where $\langle E_a\rangle = \langle E^*\rangle + \langle I\rangle$. With (9), (5) can be rewritten as

$$k_{ij} = k_\circ \exp\left[\frac{\alpha\Delta I_i - (1-\alpha)\Delta I_j}{k_BT}\right], \tag{10}$$

where $k_\circ = \nu\exp(-\langle E_a\rangle/k_BT)$.

Taken together, Eqs. (4) and (10) can be used as a basis for general calculations illustrating the likely specifics of the late state of the PC formation. In such calculations, it is convenient, however, to employ the probabilities $p_i = n_i/n_{\rm tot}$ to find specific proteins in PC ($n_{\rm tot}$ is the total number of proteins in PC) and to represent the protein concentrations in solution as $c_i = \beta_i c_{\rm tot}$, where $c_{\rm tot}$ is the total concentration, and β_i is the dimensionless fraction of protein i (with $\sum_i \beta_i = 1$). In these terms, Eq. (4) can be rewritten as

$$\frac{dp_i}{dt} = c_{\rm tot}\sum_{j\neq i}(k_{ij}\beta_i p_j - k_{ji}\beta_j p_i). \tag{11}$$

Equations (10) and (11) form a basis for the calculations presented below.

To complete this general section, it is instructive to scrutinize the model predictions under steady-state conditions, $dp_i/dt = 0$. In this case, the solution of (11) directly follows from the detailed balance, $k_{ji}\beta_j p_i = k_{ij}\beta_i p_j$. Using (10), this condition can be rewritten as

$$p_i/[\beta_i\exp(\Delta I_i/k_BT)] = p_j/[\beta_j\exp(\Delta I_j/k_BT)]$$

and should be fulfilled for arbitrary i and j. This means that the ratio of p_i and $\beta_i\exp(\Delta I_i/k_BT)$ should be the same for each i, i.e., $p_i/[\beta_i\exp(\Delta I_i/k_BT)] = \text{const}$, or $p_i = \text{const}\,\beta_i\exp(\Delta I_i/k_BT)$. As expected, the latter expression corresponds to the grand canonical distribution. The constant in these relations can be obtained by employing the normalization condition. This yields

$$p_i = \beta_i\exp(\Delta I_i/k_BT)\Big/\sum_j \beta_j\exp(\Delta I_j/k_BT). \tag{12}$$

The grand canonical distribution is independent of the specific details of the kinetics, and accordingly, as one could expect, distribution (12) is the same as, e.g., that given by the Langmuir isotherms for coadsorption in the limit of high coverage. This means that at $t\to\infty$, the exchange and Langmuir models cannot be distinguished. In experiments, this limit is, however, usually not reached.

III. RESULTS OF CALCULATIONS

The model introduced is focused on the late stage of the PC formation. In the examples of the use of this model below, $t = 0$ is associated with the beginning of this stage, and the corresponding kinetics are calculated as a function of the dimensionless time defined as $\tau = k_\circ c_{\rm tot} t$.

In the model, proteins are characterized by the binding-energy deviations, ΔI_i. To perform calculations, it is convenient to divide proteins into the subpopulations with nearly the same binding energies so that the difference between the average energies of two nearest-neighbor subpopulations is equal to A. This discretization yields

$$\Delta I_i = A\,i, \tag{13}$$

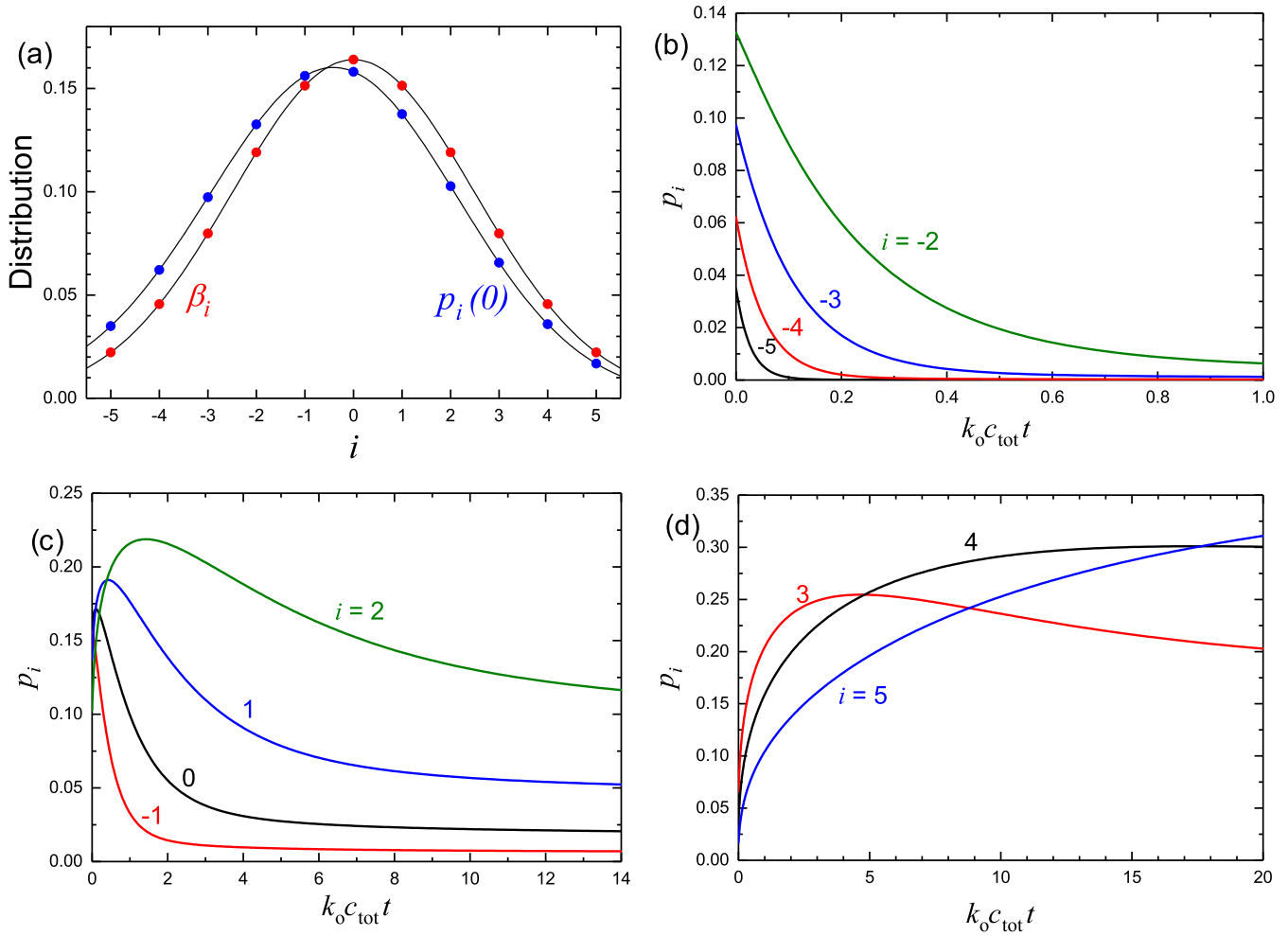

FIG. 1. (a) Protein distributions β_i and $p_i(0)$ (filled circles) according, respectively, to Eqs. (16) and (15) with $n = 5$, $\sigma = 8$, and $B = 2/25$, and [(b)–(d)] the corresponding kinetics of the late stage of the PC formation according to Eq. (11).

where i is an integer in the range from $-n$ to n so that the total number of subpopulations is $2n + 1$. In the calculations presented, I employ $A = k_B T$ and $n = 5$ in order to specify ΔI_i [Eq. (13)] and $\alpha = 1/3$ in order to specify the dependence of k_{ij} on ΔI_i [Eq. (10)].

In addition, I need the initial distribution, $p_i(0)$, of the attached proteins in the beginning of the late stage (at $t = 0$). It depends on the specifics of the protein adsorption kinetics at the initial stage (at $t < 0$). During this stage, the protein attachment is controlled by diffusion, and the populations of proteins at NPs are proportional to their distribution, β_i, and diffusion coefficients, D_i, in solution. *In vivo*, this stage is usually rapid and results in almost complete coverage of NPs by proteins. Taking these factors into account, I consider that NPs are fully covered by proteins at $t = 0$ and that the initial distribution of the attached proteins is given by

$$p_i(0) = D_i \beta_i \Big/ \sum_j D_j \beta_j. \tag{14}$$

To use this expression, one should specify the dependence of D_i on i. By definition [Eqs. (7) and (13)], i characterizes the deviation of the binding energy from the average for protein i. By analogy with (13), the binding energy itself can be represented as $I_i = A(\sigma + i)$, where $A\sigma$ is the average value. Physically, the binding energy is expected to be proportional to the protein-support contact area which in turn can be considered to be approximately proportional to the average protein cross section or to the square of the protein radius, R_i^2. This means that $R_i \propto (\sigma + i)^{1/2}$. According to the Stokes-Einstein equation, $D_i \propto 1/R_i$, or $D_i \propto 1/(\sigma + i)^{1/2}$. Using the latter relation, Eq. (14) can be rewritten as

$$p_i(0) = (\sigma + i)^{-1/2} \beta_i \Big/ \sum_j (\sigma + j)^{-1/2} \beta_j. \tag{15}$$

With discretization (13), the fractions β_i characterize the distribution of proteins in solution with respect to their energy of binding to NPs and accordingly depend on the distribution of subpopulations of different proteins in solution and the type of NPs. In real biofluids, the number of protein subpopulations is large, and the former distribution is still poorly known. For this reason, I axiomatically introduce three qualitatively different distributions β_i and show the late stage of the corresponding PC formation kinetics.

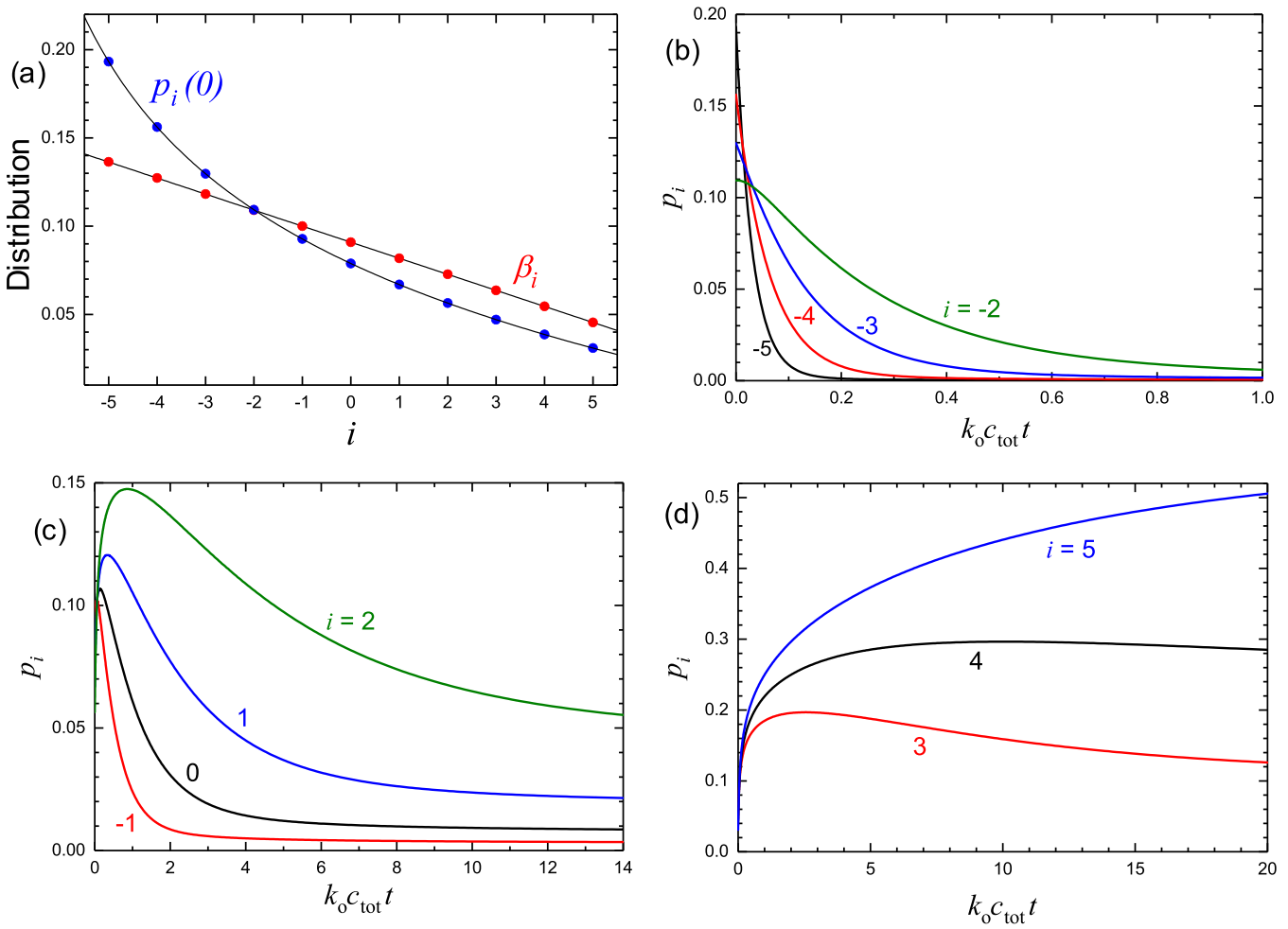

FIG. 2. As Fig. 1 for linear distribution (17) with $B < 0$.

The first (Gaussian) distribution of proteins in solution,

$$\beta_i = C \exp(-Bi^2) \text{ with } C = 1 \Big/ \sum_{i=-n}^{i=n} \exp(-B\, i^2), \quad (16)$$

is chosen to be symmetric with respect to $i = 0$ [Fig. 1(a)]. In this case, the late stage of the PC formation is started by relatively rapid replacement of weakly bound proteins [with $i \leqslant -2$; Fig. 1(b)] primarily by proteins (with $i = 0$, 1, and 2) which are most abundant in solution. The fractions of the latter proteins in PC first accordingly rapidly grow but then start to drop slowly [Fig. 1(c)] due to their replacement by proteins with largest binding energies [$i = 3$, 4, and 5; Fig. 1(d)]. On the timescale of the full redistribution of proteins with largest binding energies, the corresponding initial growth of their fractions is relatively rapid [Fig. 1(c)]. Their subsequent redistribution is appreciably slower.

The second (linear) distribution,

$$\beta_i = B\, i + C \text{ with } C = 1/(2n+1), \quad (17)$$

is chosen to decrease monotonously with increasing i [Fig. 2(a)] so that the proteins with low binding energy are most abundant in solution (this is the case provided $B < 0$). In this case, the PC-formation kinetics [Figs. 2(b)–2(d)] are qualitatively similar to those shown in Figs. 1(b)– 1(d).

The third (linear) distribution [Eq. (17)] is considered to increase monotonously with increasing i [Fig. 3(a)] so that the proteins with large binding energy are most abundant in solution (this is the case provided $B > 0$). Here the results [Figs. 3(b)–3(d)] are qualitatively similar to those shown in Figs. 1(b)– 1(d) as well.

Quantitatively, one can notice that the ratio of the timescales of the kinetics shown in panels (d) and (b) of Figs. 1–3 becomes smaller with the transition from the first distribution (Fig. 1) to the third distribution (Fig. 3). Concerning the protein distribution in PC in the end, the general trend is that the proteins with larger binding energy ($i = 5$) dominates but in different extent. In the first distribution [Fig. 1(d)], the domination is nearly negligible (the populations with $i = 3$, 4, and 5 are comparable) because the binding-energy-related preference in adsorption is almost compensated by rapid decrease of β_i with increasing i for large i [Eq. (12)]. In the third distribution [Fig. 3(d)], the domination is appreciable because both factors are in favor of the population with $i = 5$.

In the calculations presented above, the initial distribution of the attached proteins was considered to be proportional to D_i and β_i [Eqs. (14) and (15)]. D_i is inversely proportional to the protein radius, and accordingly the distribution of D_i is narrower than that of β_i. In principle, the dependence of the initial distribution of the attached proteins on D_i can be

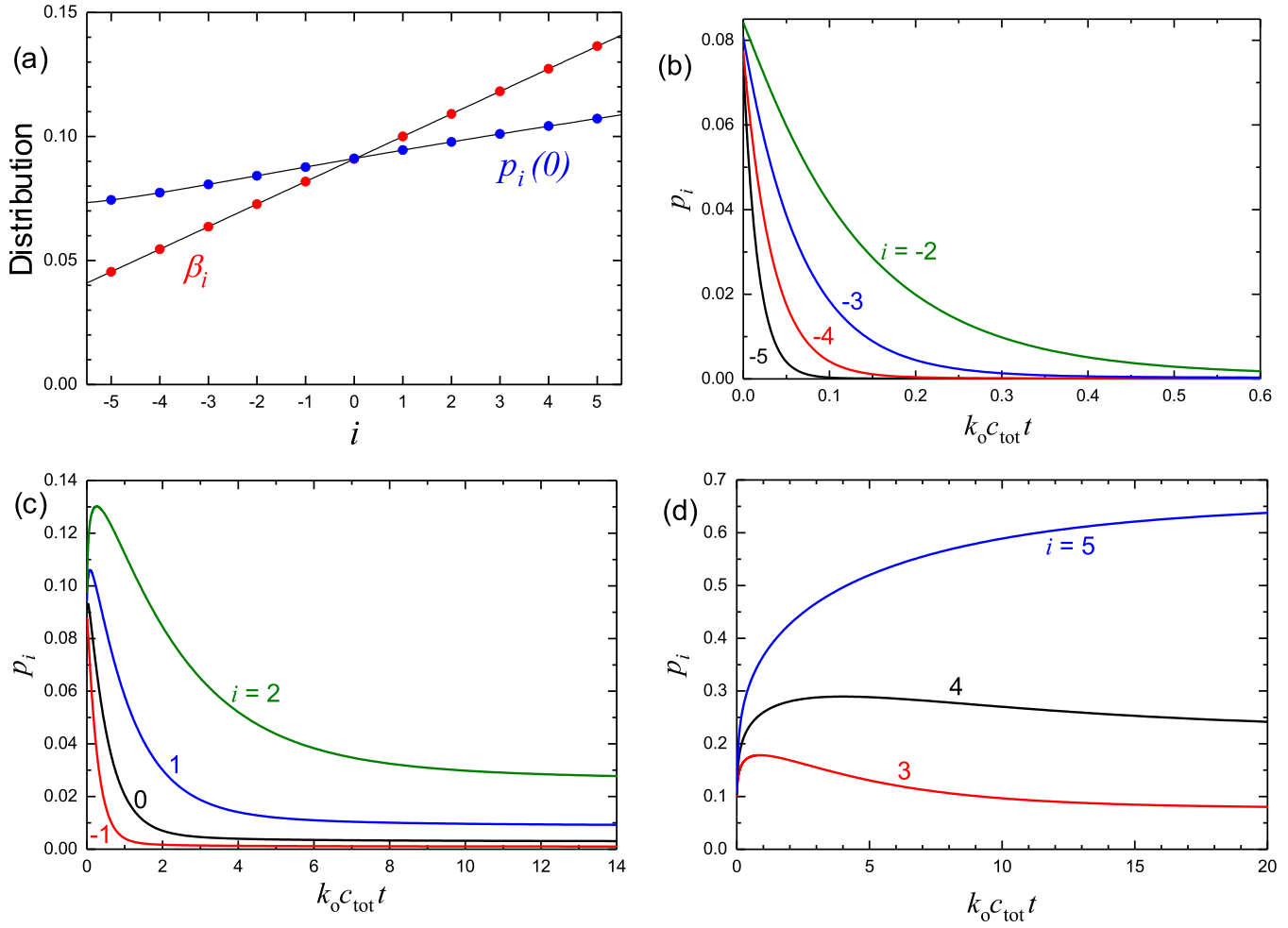

FIG. 3. As Fig. 1 for linear distribution (17) with $B > 0$.

neglected, i.e., one can use

$$p_i(0) = \beta_i. \tag{18}$$

Keeping the same values of the parameters, I have performed the calculations of the kinetics of the PC formation with the latter initial condition as well. The corresponding results [37] are close to those shown in Figs. 1– 3.

IV. CONCLUSION

My analysis has been focused at the late stage of the PC formation. Its importance and some implications for experiments are clear from the Introduction and Secs. II and III. More explicitly, the key elements can be outlined as follows.

(i) I have presented arguments in favor of appreciable role of the exchange in redistribution of proteins attached to NPs. From conventional experimental and theoretical studies of protein adsorption at macroscopic samples, the impression might be that this mechanism is rare and inferior. This impression appears, however, to be incorrect simply because conventional studies are rarely focused on the very late stage of competitive adsorption of two or more proteins. In the experimental and theoretical studies of the PC formation, the exchange mechanism is usually not mentioned. Under such circumstances, in fact, my analysis introduces the concept of exchange into the studies of the PC formation.

(ii) The way to describe the protein exchange in the case of presence of proteins of very different types with a broad distribution of adsorption energies is not obvious and was earlier not discussed. I have motivated the use of the Evans-Polanyi-type relation between the activation energies of the protein-exchange steps and protein binding energies.

(iii) My calculations were obtained for three qualitatively different distribution of proteins in solution over binding energy. In all the cases, the kinetics under consideration are shown to be similar with rapid relatively rapid replacement of weakly bound proteins and slow redistribution of strongly bound proteins. The ratio of the timescales characterizing the evolution of weakly and strongly bound proteins is, however, found to depend on the type of the distribution of proteins in solution over binding energy.

My analysis and calculations are fully phenomenological and, taken alone, do not allow one to conclude whether or not the exchange mechanism is really operative during the late stage of the PC formation. Unfortunately, the qualitative features summarized in item (iii) above are not too specific, and apparently similar features can in principle be observed in the case of conventional mechanism of protein adsorption as well. This means that the discrimination of the mechanisms should

be more based on quantitative data. One of the obvious options is to compare the timescales of reaching a real or apparent steady state for adsorption of specific proteins during the late stage of the PC formation with the timescales characterizing their detachment. In fact, my arguments in the Introduction follow this line with emphasis on albumin adsorption on SiO_2. Unfortunately, the full-scale realization of this option is far from straightforward because now such data for many other proteins are lacking (see, e.g., already-mentioned comprehensive studies [13,14] and more recent reports [38–42]). In the case of biofluids containing numerous protein species, the corresponding measurements are in principle possible but in reality are challenging and time-consuming. The first reasonable step is to scrutinize the likely role of the exchange in the late stage of adsorption in solutions containing two or three protein species which are abundant in biofluids. Following this line, I can, e.g., briefly discuss two examples already mentioned in the Introduction.

As the first example, I repeat that Vilanova *et al.* [8] have observed that on SiO_2 NPS the preadsorption of human serum albumin and transferrin followed by adsorption of fibrinogen the former two proteins were replaced by the latter one on the timescale somewhat shorter or about 10 min. The corresponding kinetics were described by using the conventional model with the coverage-dependent rate constants for desorption. The values of these rate constants and the type of the coverage dependence were fitted. In this context, it is of interest that the independent detailed studies of adsorption and desorption of human serum albumin on SiO_2 (Figs. 2 and 5 in Ref. [19] and Fig. 3 in Ref. [20]) show that the desorption occurs on a timescale much longer than 10 min. This is indicative that one cannot exclude that the desorption of albumin and transferrin induced by fibrinogen as observed in Ref. [8] can mechanistically occur via exchange.

As the second example, I notice that the experiments by Tenzer *et al.* [13] show that in the SiO_2 NP case albumin is abundant both in the plasma and PC, whereas the second most abundant plasma protein, α-2-macroglobulin, is only the 13th in PC. One of the explanations of this observation might be that there is exchange of α-2-macroglobulin by albumin or some other proteins dominating in PC, and this can be verified in independent experiments.

Finally, I may repeat (cf. Sec. I) that the challenge of full-scale studying of the formation of PC biofluids is to some extent similar to that in the areas of genetic and neural networks (concerning these networks, see, e.g., Refs. [28,43,44] and [29,45,46], respectively, and references therein). In all these cases, the system diversity is huge, there is complex interplay of elements, and the links between the models and experiment are often not direct. Compared to the PC formation, the history of studies in the latter two areas is much longer, and it shows that although the subjects appear to be exhaustless the progress is possible, and at the conceptual level it is partly related to the generic models.

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