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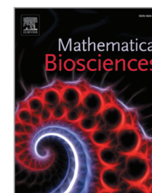

Kinetics of the formation of a protein corona around nanoparticles

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ABSTRACT

Interaction of metal or oxide nanoparticles (NPs) with biological soft matter is one of the central phenomena in basic and applied biology-oriented nanoscience. Often, this interaction includes adsorption of suspended proteins on the NP surface, resulting in the formation of the protein corona around NPs. Structurally, the corona contains a "hard" monolayer shell directly contacting a NP and a more distant weakly associated "soft" shell. Chemically, the corona is typically composed of a mixture of distinct proteins. The corresponding experimental and theoretical studies have already clarified many aspects of the corona formation. The process is, however, complex, and its understanding is still incomplete. Herein, we present a kinetic mean-field model of the formation of the "hard" corona with emphasis on the role of (i) protein-diffusion limitations and (ii) interplay between competitive adsorption of distinct proteins and irreversible reconfiguration of their native structure. The former factor is demonstrated to be significant only in the very beginning of the corona formation. The latter factor is predicted to be more important. It may determine the composition of the corona on the time scales comparable or longer than a few hours.

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1. Introduction

Adsorption of proteins on solid surfaces is studied already several decades (reviewed in [1–8]). The general concepts used to interpret the corresponding kinetics are considered to be well established and can be summarized as follows:

(i) The size of proteins is relatively large (a few nm) and the coefficients of protein diffusion, determined in solution by hydrodynamics, are low, while the adsorption process itself is often rapid, because the corresponding activation energy is usually small; and accordingly the whole adsorption process and especially its onset is often globally controlled by protein diffusion [8].

(ii) Adsorption of proteins is accompanied by the reconfiguration of their native structure. This process may be reversible (for the corresponding models, see e.g. Ref. [9] or Section 5.2 in review [4]). Often, it occurs rapidly during adsorption and/or just after adsorption, the corresponding changes of the protein structure may me modest, and mechanistically it can be included into the adsorption step. Alternatively, the reconfiguration may me appreciable (up to full denaturation) and take place on the time scale much longer than that characterizing the onset of adsorption. Under such circumstances, it should mechanistically be described as a distinct step characterized by its own rate constant (as it was first done by Lundström [10]).

(iii) On the time scale of conventional experiments, diffusion of adsorbed proteins is usually relatively rapid (the diffusion length is larger than the protein size) [11]. Mechanistically, this process is expected to include local temporal rearrangements of the protein structure.

(iv) One of the consequences of reconfiguration and surface diffusion of adsorbed proteins is that with increasing coverage the already adsorbed proteins may adjust their location and structure for additional adsorption of newly arriving proteins. This costs energy and collectively can be described in terms of lateral protein–protein interactions (i.e., the interactions along the surface), which influence the protein binding energy as well as the activation energy for adsorption. Direct electrostatic interaction between charged parts of adsorbed proteins can also contribute to their lateral interaction.

(v) Adsorption of proteins is reversible and eventually accompanied by their desorption. The latter process may, however, be slow (especially if the denaturation is appreciable), and on the time scale of a given experiment the adsorption may be apparently irreversible.

(vi) In the case of coadsorption of proteins, the whole process starts by adsorption of the proteins with the highest adsorption rate. Such proteins are usually relatively small and

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their binding energy is relatively low. The binding energy of proteins with larger size and smaller adsorption rate is often higher. Thermodynamically, the adsorption of the latter proteins is more favorable. For this reason, the initial high uptake of the proteins with low binding energy eventually starts to decrease due to the loss of competition for the binding site, and their final uptake may be appreciably smaller than the maximum one. This feature of protein coadsorption kinetics is referred to as the Vroman effect [12,13].

With the rapid development of nanoscience during the past decade, the interaction of proteins with metal (e.g., gold), oxide (e.g., silica and titana) and chemically fabricated (e.g., polystyrene) NPs has attracted appreciable attention due to interesting basic features, various potential applications of NPs, including e.g., targeted drug delivery, hyperthermia therapy, contrast imaging, fabrication of virus-like particles, and resolution of the potential threat of nanotechnological devices to organisms and the environment (reviewed in [14–21]; see also a recent article by Chen et al. [22]). In biological fluids, adsorption of selected proteins on such NPs results in the formation of the so-called protein corona that dramatically influences the function of NPs in biological systems. The onset of this process is usually very fast, but the whole process may take many hours or days due to slow reconfiguration and exchange of proteins at high coverage. Many related experiments were focused on the structure and composition of the corona formed after a certain interval of time (typically from about one hour to a few days). Structurally, the corona was found to contain a "hard" part, consisting of a near-monolayer of strongly bound proteins, and a "soft" part located on top and consisting of a weakly associated and rapidly exchanging layer of proteins. In practically important situations (e.g., in human blood plasma [23]), the number of distinct proteins is large but, due to the competition for the binding sites, the corona typically contains only some of them. In the case of silica NPs in blood plasma, for example, the corona consists primarily of 20 proteins (see Table 1 in [15]).

Detailed experimental studies of the kinetics of the corona formation are still not numerous (see, e.g., Refs. [24–28]). The focus is typically on the dependence of the integral protein uptake on time, because the tools to track the composition of the corona as a function of time are still limited. The experiments resolving the temporal populations of individual proteins are just beginning [27]. The available models of the kinetics of the corona formation (reviewed in [29,30]) are of two complementary categories including, respectively, coarse-grained atomistic simulations with emphasis on the dynamical aspects [31–34] and conventional mean-field (MF) kinetic models focused on the "hard" part of the corona with emphasis on competitive adsorption [35,36] or on the "soft" part [37].

In general, the kinetics of the formation of a protein corona around NPs depend or may depend on numerous factors. Herein, we present a general MF kinetic model of the formation of the "hard" part of the protein corona (Section 2). Compared to the already available models, it scrutinizes in more detail the onset of the kinetics or, more specifically, the role of diffusion limitations (Section 2) and the final stage of the kinetics with the interplay between competitive adsorption, desorption and irreversible reconfiguration of different proteins (Section 3). From various points of view (e.g., in applications), the final stage of the kinetics is more important than the onset. The reconfiguration of some of the proteins during the final stage of the kinetics is expected to take place if the protein binding energy is significant. This is often the case for metal and oxide NPs. For this reason, our model is oriented to metal and oxide NPs. The model itself is relatively simple and makes it possible to understand likely general trends in the kinetics under consideration. The cumbersome details related to diffusion limitations are given in Appendix A and may be omitted if one is not interested in math. The expected scale of deviations from the MF approximation at high coverage is illustrated in Appendix B by using Monte Carlo (MC) simulations (this Appendix may be omitted as well if one is not interested in math). Focusing on the general interplay of the kinetic steps, we do not take into account many specific factors which may be important for specific nanoparticles and/or proteins. Some of such factors are briefly discussed in Section 4. Finally, we summarize our key findings in Section 5.

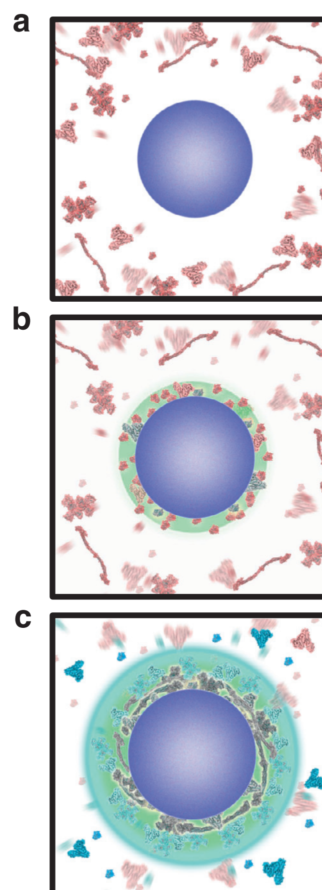

Fig. 1. Schematic view of the formation of the hard protein corona around a nanoparticle in blood plasma. The panels show the cross section of a nanoparticle surrounded by adsorbed proteins. For the sake of simplicity, the proteins exhibited include only Fibrinogen (large sized protein), Vitronectin and Human Serum Albumin (intermediate sized), and Cytochrome C (small sized proteins). The whole process is divided into three stages: (a) a nanoparticle is introduced into plasma, (b) smaller proteins (HSA and Cyt C) adsorb first and some are denatured, and (c) eventually, larger proteins replace the smaller ones (Vroman effect) and then undergo denaturation to achieve irreversible adsorption. Native plasma proteins are represented in red (online). Denatured adsorbed proteins are shown in gray. Desorbed proteins are represented in blue. The hard corona is emphasized with a green halo. The soft corona is differentiated by a cyan colored halo (with associated proteins in the same color). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2. General equations

In our model, a NP is considered to be spherical (Fig. 1). The adsorption of each protein is described in the two-state approximation (as originally proposed by Lundström [10] and reviewed in Ref. [8]), i.e., a protein is considered to be adsorbed either in the native or in the altered (denatured) state. The transition kinetics from the former to the latter state is assumed to be irreversible and to obey the first-order law with a correction taking saturation of the adsorbed overlayer into account. Reconfiguration of

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