Modeling of a single nanoparticle interaction with the human blood plasma proteins

Vladas Skakauskas¹ · Pranas Katauskis¹

Received: 21 November 2017 / Accepted: 13 August 2018 / Published online: 12 September 2018
© Springer Nature B.V. 2018

Abstract

When nanoparticles are introduced into a physiological environment, proteins and lipids immediately cover their surface, forming a protein “corona”. It is well recognized that the corona structure influences the biological response of the body. Two deterministic models for corona formation of the human blood serum proteins around a single nanoparticle are presented and studied numerically in this paper. One of them is based on a coupled system of PDEs and involves diffusion of proteins toward the nanoparticle surface. The other one is described by ODEs and is a limit version of the first model as the protein diffusivity tends to infinity. The protein diffusivity influence on the temporal corona structure is studied in detail. Results are presented using figures and discussion.

Keywords Nanoparticle · Protein binding · Protein corona · Nanotoxicity

1 Introduction

Nano-sized materials are widely used in a variety of biomedical applications ranging from cellular imaging to drug and vaccine delivery [1, 2]. Upon intravenous injection, numerous blood plasma proteins and lipids immediately begin competitive adsorption on the surface of nanoparticles. It is well documented that the most abundant and highly mobile but weakly adsorbing proteins adsorb on the particle surface in the initial stage. However, over time, by series of adsorption and displacement steps they will be replaced by strongly adsorbing proteins [3–6]. Competitive protein adsorption from blood plasma (or another multicomponent solution) onto the surface of nanoparticles depends on different factors such as protein concentrations, their chemical structure and charge, the temperature, and the pH [7, 8]. The adsorbed proteins and lipids form a so-called protein “corona”, whose composition depends on physico-chemical characteristics of the nanoparticles (shape, size, curvature, surface charge, hydrophobicity, hydrophilicity) [9–12] and proteins and varies over time. The protein corona alters these physico-chemical characteristics of nanoparticles and thereby forms

✉ Vladas Skakauskas
vladas.skakauskas@mif.vu.lt

¹ Faculty of Mathematics and Informatics, Vilnius University, Naugarduko 24, LT-03225 Vilnius, Lithuania

a new biological identity that determines the physiological cellular response, including kinetics, transport, accumulation, circulation lifetime, cellular uptake, toxicity, and biodistribution of nanoparticles throughout the body [1, 13]. Thus, a deep understanding of the protein corona formation process is key in studying the biological effects of nanoparticles [4]. Numerous papers and reviews are devoted to the experimental and theoretical study of possible driving forces in the corona formation process and their modeling. The eventual goal of these studies is to predict the composition of proteins in the corona, depending on their composition in the given multicomponent solution [14]. We will mention reviews [1, 14] and some recent papers devoted to experimental study and computer simulations. Two mathematically simple corona formation models described by systems of ordinary differential equations (ODE) with experimentally measured kinetic rate constants have been proposed in [15, 16]. Recent studies revealed that protein adsorption on the surface of nanoparticles is mostly driven by global electrostatic and local hydrophobic–hydrophilic interactions (see [8] and literature therein). Models [15, 16] are based on the mass action law and the Langmuir approach, respectively, and neglect the electrostatic protein–protein interaction, hydrophobic–hydrophilic effects of the surface, and volume changes during adsorption [8].

In [17], the diffusion-controlled protein binding to negatively charged colloidal particles is modeled by employing a two-step Langmuir approach where the protein diffusion region is divided into two subregions: (i) a layer between the nanoparticle, and a sphere of an overall hydrodynamic radius and (ii) an external bulk diffusion subregion. However, the protein diffusion equations are not incorporated into this model. The protein adsorption rate constant is modeled as a function of the protein bulk diffusivity in the external subregion and its internal diffusivity. The latter is an unknown parameter.

A model accounting for the deformation of semipermanently adsorbed proteins has been proposed in [18]. Authors of [7, 8] demonstrated that in the case of adsorption equilibrium, the electrostatic cooperativity and hydrophobic effects and volume changes can be introduced into standard Langmuir adsorption models using the Guoy–Chapman–Stern theory [19–21] for charged molecules binding to charged surfaces. This approach and that used in [15–17] are based on the continuum description. To describe the electrostatic protein–protein and protein–nanoparticle interaction directly, computer simulations based on the Langevin equation [22, 23] and a coarse-grained approach [7, 8, 24, 25] have been developed. The conformational changes of fibrinogen adsorption from “lying down” to “standing up” have also been included into model [24] describing the ternary protein mixture interaction with a hydrophobic surface. However, the coarse-grained approach allows us to perform simulations for binary and ternary protein solutions up to 10 s. In paper [25], a model based on the mass action law with kinetic coefficients depending on each protein surface coverage and concentration of nanoparticles and proteins has been proposed for large time scales.

In [15–17], the protein corona formation around a set of copolymer nanoparticles and its dynamics have been studied assuming that protein molecules and nanoparticles at every moment are distributed homogeneously in the space. This means that protein molecules diffuse to nanoparticles at an infinite rate. In models [15, 16], the protein molecules have been modeled as rigid spheres with the adsorption sites number dependent on the protein kind. However, these two models do not allow us to determine the fraction of the surface of the given nanoparticle covered by molecules of the specific protein, i.e., they do not allow to determine the corona structure of the given nanoparticle directly. The approach used in these studies also does not allow one to study the diffusion of the corona–nanoparticle complexes.

In the present paper, neglecting the hydrophobicity–hydrophilicity of the nanoparticle surface and volume changes and surface diffusion of the adsorbed protein molecules, we

present and study a model of the protein corona formation around a single nanoparticle using the continuum approach. To do this, we extend the model [16] by incorporating protein diffusion equations and study the diffusion influence on concentrations of the adsorbed proteins onto the surface of a single copolymer nanoparticle. The model is described by a coupled system of partial and ordinary differential equations and directly accounts for the bulk diffusion of the protein molecules from a given region toward the nanoparticle. The protein–protein interaction has been included into equations indirectly (via the protein concentration-dependent diffusion rate). We account for the electrostatic protein interaction with the nanoparticle surface by experimentally measured adsorption rate constants that are given in [15]. To compare our results determined by the model for a single nanoparticle with those given in [15, 16] for a mixture of nanoparticles and some kinds of proteins and to obtain results for very large (practically infinite) diffusivity, we derive and solve the other model mathematical equations, which are analogous to those proposed in [16]. This second model, as well those given in [15, 16], are described by ODEs. It is derived from the first one by using an averaging procedure and corresponds to the first model with the infinite diffusion rate.

The plan of this paper is as follows. In Section 2, we describe the models. In Section 3, we discuss numerical results, and concluding remarks are found in Section 4.

2 The models

In this section, we present two models for the corona formation of proteins P_i , $i = 1, \dots, n$, around a single nanoparticle. One of them is described by a coupled system of partial and ordinary differential equations (below referred to as the PDE model) while the other one is composed of ODEs (referred to as the ODE model).

We first study the PDE model. For simplicity, we model protein P_i molecules as rigid spheres of radius r_i , $i = 1, \dots, m$, and assume that molecules of all proteins P_i are delivered in the domain lying between the spherical nanoparticle of radius r_c and the outer concentric sphere of radius r_e . In what follows, we study the case of spherical symmetry. We denote $p_i(t, r)$ and $u_i(t, r)$ concentrations of free and bound to the nanoparticle molecules of protein P_i , $i = 1, \dots, m$, respectively, at time t and position r . Following [15], we define the number of adsorption sites for protein P_i molecules on the nanoparticle surface by $N_i(r_i) = 4\pi(r_c + r_i)^2/(\pi r_i^2)$. Then, $n_i(r_i) = 1/(\pi r_i^2)$ is the density of the adsorption sites for protein P_i molecules. We use Fick's law with concentration-dependent diffusivity for the diffusion description of protein P_i , $i = 1, \dots, m$, molecules toward the nanoparticle surface and the law of mass to obtain the PDE model:

$$\left\{ \begin{array}{l} \partial_t p_i = \kappa_i r^{-2} \partial_r (a(p_1, p_2, p_3) r^2 \partial_r p_i), \quad r \in (r_c + r_i, r_e - r_i), \\ p_i|_{t=0} = p_{i0}, \quad r \in [r_c + r_i, r_e - r_i], \\ \partial_r p_i = 0, \quad r = r_e - r_i, \quad t > 0, \\ \kappa_i a(p_1, p_2, p_3) \partial_r p_i = k_i p_i n_i \left(1 - \sum_{j=1}^m \frac{u_j}{n_j} \right) - k_{-i} u_i, \quad r = r_c + r_i, \quad t > 0, \\ \partial_t u_i = k_i p_i n_i \left(1 - \sum_{j=1}^m \frac{u_j}{n_j} \right) - k_{-i} u_i, \quad r = r_c + r_i, \quad t > 0, \\ u_i|_{t=0} = 0, \quad r = r_c + r_i. \end{array} \right. \quad (1)$$

Here, $a(p_1, p_2, p_3) = 1 / \sum_{j=1}^m p_j$, $p_{i0}(r)$ is the initial concentration, k_i and k_{-i} are the adsorption and desorption rate constants, $\kappa_i a(p_1, p_2, p_3)$, $\kappa_i = \text{const}$, is the protein diffusivity, $n_i \sum_{j=1}^m u_j / n_j$ is the concentration of the occupied adsorption sites for P_i molecules, $i = 1, \dots, m$, $\sum_{j=1}^m u_j / n_j$ is a surface coverage. Model (1) possesses m mass conservation laws:

$$\int_{r_c+r_i}^{r_e-r_i} r^2 (p_i(t, r) - p_{i0}(r)) dr + (r_c + r_i)^2 u_i(t) = 0, \quad t \geq 0, \quad i = 1, \dots, m. \quad (2)$$

Next, we integrate differential equations of system (1) over the 3D domain and use the boundary conditions and definition of the average function yielding the following ODE model:

$$\begin{cases} \hat{p}'_i = -\eta_i \left(k_i \hat{p}_i n_i \left(1 - \sum_{j=1}^m \frac{u_j}{n_j} \right) - k_{-i} u_i \right), & t > 0, \\ \hat{p}_i|_{t=0} = p_{i0}, \\ u'_i = k_i \hat{p}_i n_i \left(1 - \sum_{j=1}^m \frac{u_j}{n_j} \right) - k_{-i} u_i, & t > 0, \\ u_i|_{t=0} = 0 \end{cases} \quad (3)$$

where the prime denotes the derivative with respect to time and:

$$\begin{aligned} \hat{p}_i(t) &:= \frac{3 \int_{r_c+r_i}^{r_e-r_i} r^2 p_i(t, r) dr}{(r_e - r_i)^3 - (r_c + r_i)^3}, \\ \eta_i &:= \frac{3(r_c + r_i)^2}{(r_e - r_i)^3 - (r_c + r_i)^3} \end{aligned}$$

with $i = 1, \dots, m$. This model also possesses m mass conservation laws:

$$\hat{p}_i = \hat{p}_{i0} - \eta_i u_i, \quad i = 1, \dots, m, \quad (4)$$

which enable us to reduce system (3) to the equations for u_i :

$$u'_i = k_i n_i (\hat{p}_{i0} - \eta_i u_i) \left(1 - \sum_{j=1}^m \frac{u_j}{n_j} \right) - k_{-i} u_i, \quad t > 0, \quad u_i|_{t=0} = 0 \quad (5)$$

where $i = 1, \dots, m$. System (5) is formally analogous to (23) proposed in [16] and differs from them by the multiplier η_i . The essential difference is that the u_i in (5) is the surface density of the adsorbed protein molecules while (23) in [16] describe the evolution of the bulk concentrations of the adsorbed protein particles. Note that systems (3) and (5) do not depend on the protein diffusivity.

In the steady-state case, from system (1) it follows that p_i and u_i are some constants. Let $p_i^{st} := p_i$ and $u_i^{st} := u_i$. In the case where $p_{i0} = \text{const}$, from (2) and (1)₅ we find:

$$p_i^{st} = p_{i0} - \eta_i u_i^{st}, \quad u_i^{st} = \frac{k_i n_i p_{i0} x_*}{k_{-i} + k_i n_i \eta_i x_*} \quad (6)$$

where $i = 1, \dots, m$ and $x_* \in (0, 1)$ is a unique positive root of the equation:

$$1 - x = \sum_{i=1}^m \frac{k_i p_{i0} x}{k_{-i} + k_i n_i \eta_i x}. \quad (7)$$

The same result follows from (5). We observe that p_i^{st} and u_i^{st} do not depend on the protein diffusivity κ_i .

Using the dimensionless variables $\bar{t} = t/\tau$, $\bar{r} = r/r_c$, $\bar{r}_i = r_i/r_c$, $\bar{r}_e = r_e/r_c$, $\bar{r}_c = 1$, $\bar{u}_i = u_i/n_i$, $\bar{n}_i = \pi r_c^2 n_i = 1/\bar{r}_i^2$, $\bar{p}_i = p_i/p_*$, $\bar{p}_{i0} = p_{i0}/p_*$, $\bar{a} = p_* a$, $k_i = \tau k_i p_*$, $\bar{k}_i = \tau k_i / (p_* r_c^2)$, $\bar{k}_{-i} = k_{-i} \tau$, $\zeta = \pi p_* r_c^3$, $\bar{\eta}_i = r_c \eta_i$, where $i = 1, \dots, m$ and $\tau = 1$ s, r_c measured in nm, $p_* = 10^{-5}$ M with $M = 6.022 \cdot 10^{20} \text{ cm}^{-3}$ are the characteristic dimensional units, we rewrite (1) in the form:

$$\begin{cases} \partial_t p_i = \kappa_i r^{-2} \partial_r (a(p_1, p_2, p_3) r^2 \partial_r p_i), & r \in (1 + r_i, r_e - r_i), \quad t > 0, \\ p_i|_{t=0} = p_{i0}, & r \in [1 + r_i, r_e - r_i], \\ \partial_r p_i = 0, & r = r_e - r_i, \quad t > 0, \\ \kappa_i a(p_1, p_2, p_3) \partial_r p_i = \frac{1}{\zeta r_i^2} \left(k_i p_i \left(1 - \sum_{j=1}^m u_j \right) - k_{-i} u_i \right), & r = 1 + r_i, \quad t > 0, \\ \partial_t u_i = k_i p_i \left(1 - \sum_{j=1}^m u_j \right) - k_{-i} u_i, & r = 1 + r_i, \quad t > 0, \\ u_i|_{t=0} = 0, & r = 1 + r_i, \end{cases} \quad (8)$$

with $i = 1, \dots, m$ and the overbar on the quantities is omitted for simplicity.

Similarly, we derive the dimensionless form of system (3) with $\hat{p}_i$ renamed by p_i :

$$\begin{cases} p'_i = -\frac{\eta_i}{\zeta r_i^2} \left(k_i p_i \left(1 - \sum_{j=1}^m u_j \right) - k_{-i} u_i \right), & t > 0, \quad p_i|_{t=0} = p_{i0}, \\ u'_i = k_i p_i \left(1 - \sum_{j=1}^m u_j \right) - k_{-i} u_i, & t > 0, \quad u_i|_{t=0} = 0 \end{cases} \quad (9)$$

where $\eta_i = 3(1+r_i)^2 / ((r_e - r_i)^3 - (1 + r_i)^3)$, $i = 1, \dots, m$. The dimensionless equations (4)–(7) are:

$$p_i = p_{i0} - \eta_i u_i / (\zeta r_i^2), \quad (10)$$

$$u_i^{st} = \frac{k_i p_{i0} x_*}{k_{-i} + k_i \eta_i x_* / (\zeta r_i^2)}, \quad (11)$$

$$1 - x = \sum_{j=1}^m \frac{k_j p_{j0} x}{k_{-j} + k_j \eta_j x / (\zeta r_j^2)}, \quad (12)$$

$$u'_i = k_i \left(p_{i0} - \frac{\eta_i u_i}{\zeta r_i^2} \right) \left(1 - \sum_{j=1}^n u_j \right) - k_{-i} u_i, \quad t > 0, \quad u_i|_{t=0} = 0 \quad (13)$$

where $i = 1, \dots, m$.

3 Numerical results

We follow [15, 16] and perform calculations for high-density lipoprotein (HDL), human serum albumin (HSA), and fibrinogen (Fib). Let P_1 , P_2 , and P_3 be the HDL, HSA, and Fib. Our selection of parameters for simulations was motivated by values available in the literature. We use the experimentally measured adsorption and desorption rate constants, radii of proteins and nanoparticles, and initial concentrations of proteins given in Table 1 of [15]: $r_c = 35$ nm, $r_1 = 5$ nm, $r_2 = 4$ nm, $r_3 = 8.3$ nm, $p_{10} = 1.5 \cdot 10^{-5}$ M, $p_{20} = 6 \cdot 10^{-4}$ M, $p_{30} = 8.8 \cdot 10^{-6}$ M, $k_1 = 3 \cdot 10^4 \text{ M}^{-1} \text{ s}^{-1}$, $k_2 = 2.4 \cdot 10^3 \text{ M}^{-1} \text{ s}^{-1}$, $k_3 = 2 \cdot 10^3 \text{ M}^{-1} \text{ s}^{-1}$, $k_{-1} = 3 \cdot 10^{-5} \text{ s}^{-1}$, $k_{-2} = k_{-3} = 2 \cdot 10^{-5} \text{ s}^{-1}$. For diffusivity of all proteins, we use model values from a broad range to allow illustration of various regimes possible in the body.

Equation (8) was solved by using a conservative difference scheme [26] that preserves the discrete analogue of mass conservation laws (2). The validation of our simulations was also performed by comparing our results with those given in [15, 16]. To solve (10) or (13), we apply MATLAB solver ode45 [27, 28]. To find u_i^{st} we first determine x_* from (12) and then by (11) calculate u_i^{st} , $i = 1, 2, 3$. Numerical results are presented in Figs. 1, 2, 3, 4, 5, and 6 in nondimensional form.

In Fig. 1, the influence of the volume size, $(4\pi/3)((r_e - r_i)^3 - (r_c - r_i)^3)$, on the behavior of concentrations u_1 (Fig. 1a), u_2 (Fig. 1b), u_3 (Fig. 1c) of adsorbed protein P_i , $i = 1, 2, 3$, molecules is illustrated for $r_e = 4, 8, 16$ and $\kappa := \kappa_1 = \kappa_2 = \kappa_3 = 1$ (solid lines) and $\kappa_1 = 5, \kappa_2 = \kappa_3 = 1$ (dashed line). We observe a very significant influence of the variation of radius $r_e \in [4, 16]$: HDL concentration, u_1 , grows as r_e increases while concentrations of HSA and Fib, u_2 and u_3 , decrease. All curves saturate at $r_e = 16$. The thickness of the diffusion layer corresponding to this value of the r_e is about 5–8 hydrodynamic diameters of the fibrinogen molecule. Diffusivity κ_1 also strongly influences the behavior of concentrations of adsorbed protein molecules: u_1 grows while both u_2 and u_3 decrease as κ_1 increases. Function $u_1(t)$ monotonically increases over time to the asymptotic value u_1^{st} determined by (11). Concentrations $u_2(t)$ and $u_3(t)$ grow rapidly, reach maximum values, and then slowly decrease toward appropriate steady-state values u_i^{st} , $i = 1, 2$, dependent on r_e and r_i but independent of diffusivity κ_i , $i = 1, 2, 3$. Values $\max u_2 = 0.915$ and $\max u_3 = 0.0382$ achieved at $t = 25$ and $t = 21$, respectively, for $\kappa_i = 1$, $i = 1, 2, 3$, do not

Fig. 1 Effect of the outer sphere radius r_e : 4 (1), 8 (2), 16 (3), on the adsorbed protein concentrations u_i , $i = 1, 2, 3$, for $\kappa_1 = \kappa_2 = \kappa_3 = 1$ (solid line) and $\kappa_1 = 5, \kappa_2 = \kappa_3 = 1$ (dashed line)

depend on r_e . Values $\max u_2 = 0.858$ and $\max u_3 = 0.0358$ achieved at $t = 21$ and $t = 19$, respectively, for $\kappa_1 = 5, \kappa_2 = \kappa_3 = 1$ are also independent of r_e . Concentrations $u_1(t), u_2(t)$ and $u_3(t)$ for $t \in [0, 600]$ practically do not depend on r_e but for large t the influence of r_e is perceptible. Asymptotic values of $u_i, i = 1, 2, 3$, are diffusivity-independent but depend on r_e : $u_1^{st}|_{r_e=16}/u_1^{st}|_{r_e=4} = 1.93, u_2^{st}|_{r_e=16}/u_2^{st}|_{r_e=4} = 0.12, u_3^{st}|_{r_e=16}/u_3^{st}|_{r_e=4} = 0.11$.

In Fig. 2, the evolution of the adsorption region size is illustrated for diffusivity $\kappa = 10$. The depth of this region is about 6 radii of the nanoparticle. For $\kappa = 1$ its depth is about 4 of these radii. For $\kappa = 10$ concentrations p_1, p_2 and p_3 achieve minimum values 0.076, 18.33, and 0.618 at the nanoparticle surface ($r = 1$) and $t = 0.65, t = 0.765, t = 0.915$, respectively. For $\kappa = 1$, minimum values of these concentrations are 0.016, 4.829, 0.279 at $t = 2.74, t = 2.82, t = 3.4$, respectively. For $\kappa = 1$ and large time ($t \geq 476.9$ for p_2 and $t \geq 147.5$ for p_3), concentrations p_2 and p_3 exceed their initial values. Maximum values of p_2 and p_3 are 60.75 and 0.902 at $t = 2000$ and $t = 401.36$. For $\kappa = 10$ concentrations p_2 and p_3 exceed their initial values at $t \geq 154.3$ s and $t \geq 80.54$. Maximum values of p_2 and p_3 are 60.115 and 0.882 at $t = 440.35$ and $t = 225.28$, respectively. Our simulations show that concentrations determined by the ODE model do not exhibit this excess and $\min p_2(t) = 59.95, \min p_3(t) = 0.8798$ while the HDL concentration monotonically decreases to the steady-state value. Thus, the phenomenon of the increase of protein concentrations for large time going toward the nanoparticle surface is caused by the diffusion of proteins and controlled by values of their diffusivity.

Fig. 2 Evolution of the adsorption region size for diffusivity $\kappa = 10$ and $r_e = 16$. Values of radius r : 1 (1), 1.2 (2), 2 (3), 3 (4), 7 (5)

Fig. 3 Dependence of the adsorbed protein concentrations u_i , $i = 1, 2, 3$, on diffusivity κ : 1 (1), 10 (2), 100 (3), 1000 (4) for $r_e = 16$. Dashed lines correspond to u_i , $i = 1, 2, 3$, determined by the ODE model (13)

In Fig. 3, the dependence of the HDL, HSA, and Fib concentrations, u_1 (Fig. 3a), u_2 (Fig. 3b), u_3 (Fig. 3c), on diffusivity κ is illustrated. Concentration $u_1(t)$ increases as κ grows. Concentration $u_1(t)$ converges as κ grows from below to $u_1(t)$ determined by the ODE model. For large κ and small time, $u_1(t)$ grows rapidly. Concentrations $u_2(t)$ and $u_3(t)$ decrease as κ increases and converge from above to a respective concentration determined by the ODE model. Functions $u_2(t)$ and $u_3(t)$ rapidly grow as time increases, reach maximum values, and then slowly decrease to the respective steady-state value u_i^{st} , $i = 1, 2$, independently of the diffusivity. The maximum values of $u_2(t)$ and $u_3(t)$ depend on the diffusivity κ and decrease with κ increasing. The time position of the maximum value of $u_2(t)$ and $u_3(t)$ decreases with κ growing.

Fibrinogen is an elongated protein molecule that might bind to the surface of the nanoparticle with its short end thereby increasing the density of adsorption sites for P_3 [15]. Following [15], we studied the effect of radius r_3 variation on the evolution of concentrations $u_i(t)$, $i = 1, 2, 3$. The behavior of $u_3(t)$ is illustrated in Fig. 4 for $r_3 = 0.01954$, 0.06453, 0.2371 and two diffusivity values ($\kappa = 10$ and 100). These values of r_3 correspond to $N_3(0.06453)/N_3(0.2371) = 10$ and $N_3(0.01954)/N_3(0.2371) = 100$. We can see that $u_3(t)$ grows with r_3 increasing. The time location of $\max u_3(t)$ decreases as r_3 grows. In this figure, we also compare the effect of diffusivity κ at different values of r_3 . For $r_3 = 0.2371$, the $u_3(t)$ determined for $\kappa = 10$ is larger than that corresponding to $\kappa = 100$. For $r_3 = 0.06453$ and 0.01954, its evolution is mixed. For small time, the $u_3(t)$ determined

Fig. 4 Influence of radius r_3 : 0.01954 (1), 0.06453 (2), 0.2371 (3), on the adsorbed protein concentration u_3 for $\kappa = 10$ (solid line) and $\kappa = 100$ (dashed line)

for $\kappa = 10$ is smaller than concentration $u_3(t)$ corresponding to $\kappa = 100$ but for large time their behavior is opposite. Our calculations also reveal (not shown) that variation of r_3 practically does not influence the evolution of concentrations $u_1(t)$ and $u_2(t)$. This is not surprising, because values of $u_3(t)$ are small in comparison with those of $u_1(t)$ and $u_2(t)$.

In Fig. 5, the influence of the variation of the desorption rate constants k_{-1} on the corona structure determined by the ODE model is illustrated. $u_1(t)$ decreases as k_{-1} grows while $u_2(t)$ and $u_3(t)$ increase. For sufficiently large k_{-1} concentration $u_1(t)$ becomes the non-monotonic function of time (reaches a maximum value and then decreases to a steady-state value). Concentration $u_2(t)$ increases and becomes the monotone function of time. Our calculations reveal (not shown) that the behavior of $u_3(t)$ is similar to that of $u_2(t)$. Calculations also show that for sufficiently small k_{-2} concentrations $u_1(t)$ and $u_2(t)$ become

Fig. 5 Time profiles of the adsorbed protein concentrations u_1 (solid line) and u_2 (dashed line) determined by the ODE model (13) for k_{-1} : $3 \cdot 10^{-5}$ (1), $3 \cdot 10^{-4}$ (2), $3 \cdot 10^{-3}$ (3)

Fig. 6 Influence of the fibrinogen adsorption rate constants k_3 , k_{-3} and its initial concentration p_{30} on the adsorbed HSA and fibrinogen concentrations u_2 and u_3 , respectively, determined at $r_e = 16$ by the ODE model (13) for $k_3 = 0.02$, $p_{30} = 0.88$, $k_{-3} = 2 \cdot 10^{-3}$ (1); $k_3 = 0.08$, $p_{30} = 0.88$ (2), $k_3 = 0.2$, $p_{30} = 0.88$ (3), $k_3 = 0.08$, $p_{30} = 4.6$ (4), $k_3 = 0.2$, $p_{30} = 4.6$ (5) with $k_{-3} = 2 \cdot 10^{-6}$

nonmonotone and monotone time functions, respectively. Functions $u_1(t)$ and $u_2(t)$ are slightly sensitive to variation of $k_{-3} \in [2 \cdot 10^{-5}, 2 \cdot 10^{-3}]$ while $u_3(t)$ grows as k_{-3} decreases and for sufficiently small k_{-3} becomes the monotone time function.

Figure 6 illustrates the influence of the fibrinogen adsorption rate constants k_3 and k_{-3} and its initial concentration p_{30} on the corona temporal composition. Concentration of the adsorbed HSA, $u_2(t)$, decreases as the adsorption rate constant of fibrinogen, k_3 , or its initial concentration, p_{30} , grows if other parameters are taken from Table 1 of [15]. Variation of the same parameters illustrates the monotonic increase of the fibrinogen concentration, $u_3(t)$. Simulations reveal (not shown) that the HDL concentration, $u_1(t)$, corresponding to parameters of third, fourth, and fifth curves of Fig. 6 grows, reaches maximum at $t = 8546$, 5883 , 4560 , respectively, and then slowly decreases to the corresponding steady-state value. At the initial stage, $u_2(t)$ is larger than $u_3(t)$ but over time, the adsorbed fibrinogen becomes prevailing. These results clearly demonstrate the Vroman effect.

Discussion Despite various experiments, there is no general model for the description of competitive (or cooperative) protein adsorption onto particles and surfaces. The models based on the kinetic equations are useful for a qualitative description of the experimental data by fitting the rate constants [24]. The Langmuir approach with permanent adsorption/desorption rate constants or rates dependent on each protein surface coverage and concentration of nanoparticles describes only a single (monomolecular) layer of adsorbed molecules and does not include directly the mutual interaction of the adsorbed molecules and their interaction with molecules composing the multiple layers. To study the driving forces of competitive protein adsorption from a ternary mixture composed of HSA, fibrinogen (Fib), and immunoglobulin G (IgG) on a hydrophobic surface the molecular dynamics simulations were used in [24]. Simulations performed for concentrations 4.25 g dl^{-1} , 0.325 g dl^{-1} and 1.25 g dl^{-1} of HSA, fibrinogen, and immunoglobulin G, respectively, show that the Fib concentration monotonically increases over time and exceeds the HSA and IgG concentrations. Authors of [24] stressed that the monotonic growth of the fibrinogen concentration contradicts the experimental data according to which this function reaches a maximum and then slowly decreases to a steady-state value.

The competitive adsorption of proteins from a ternary mixture composed of HSA, IgG, and Fib at different plasma polymer surfaces representing a different surface charge and hydrophobicity was investigated in [29]. On PP-DACH, representing a positively charged hydrophilic surface, the Fib dominance was observed. On the negatively charged hydrophilic PP-AA surface, the initial corona was built up by HSA, but over time the Fib prevails over HSA and HDL. At the hydrophobic PP-HMDSO surface in the early stage, the dominating protein was HSA but for large time the IgG prevailed. Investigation [15] of the competitive adsorption of proteins from a mixture composed of HSA, HDL, and Fib (with geometric and kinetic data given in Table 1 of [15]) at 50:50, NIPAM/BAM copolymer nanoparticles reveal that at the initial stage the HSA was prevailing but over time the HDL wins against HSA. The influence of the Fib radius, r_3 , on the early corona composition studied in [15] shows that a decrease of the Fib size increases the Fib concentration, u_3 , in the corona. For $r_3 = 0.2371$ and 0.06453 , the HDL concentration, u_1 , is larger than that of Fib but for $r_3 = 0.01954$ the Fib wins against the HDL in the early corona. Model [16] and the ODE model (13) with the same data as in [15] show that u_1 is larger than u_3 for all time. The different influence of the fibrinogen radius, r_3 , on the behavior of concentration $u_3(t)$ determined by [15] and models [16] and (13) lies in the difference of the models.

Results of [15] show that the temporal corona composition of a given nanoparticle strongly depends on the adsorption/desorption rate constants of each protein and initial protein concentrations. Simulations of [15] also reveal that using the same experimentally measured equilibrium affinity but different combinations of association and dissociation rate constants determines completely different corona composition in which HDL prevails over the HSA and Fib even in the early stage. Therefore, results based on the experimentally measured equilibrium affinity should be critically considered. Works [29] and [15] illustrate the Vroman effect very well and show that the corona structure (temporal and steady-state) essentially depends on the physico-chemical characteristics (shape, size, surface charge, hydrophobicity, hydrophilicity) of nanoparticles. Our results determined by the ODE model are fully consistent with those given in [16].

4 Conclusions

In this paper, two phenomenological models for protein–nanoparticle corona formation are proposed and studied numerically in the case of spherical symmetry. One of them (system (1)) is based on a coupled system of partial and ordinary differential equations. This model accounts for the particle–particle interaction indirectly (via protein concentration-dependent diffusion rates). The protein molecules interaction with the nanoparticle surface is also included indirectly (via experimentally measured adsorption/desorption rate constants given in Table 1 of paper [15]). The nanoparticle and protein molecules are modeled as rigid spheres. Protein conformational and volume changes during adsorption and hydrophobic/hydrophilic surface effects are neglected. The other model (system (3)), derived from the first one by using an averaging procedure, is analogous to that proposed in [16] and is used for comparison of our results with those given in [16]. The influence of the protein diffusivity and fibrinogen adsorption/desorption rate constants and its initial concentration on the temporal corona structure is studied. To conclude the paper, we summarize the main results:

- (i) the corona structure (transient and steady-state) depends on the size of the domain where proteins are located, but there exists a limit domain size $d = r_e^* - r_c$ ($r_e^* \approx 16r_c$,

d is about 15 radii of a nanoparticle) such that a $r_e > r_e^*$ practically does not affect the corona structure for all κ . For kinetic parameters and initial protein concentrations taken from Table 1 of [15] concentrations of HSA, $u_2(t)$ and Fib, $u_3(t)$, rapidly grow as time increases, achieve maximum values, and then slowly decrease to the steady-state values depending on $r_e < r_e^*$. The maximum values do not depend on the domain size. The HDL concentration, $u_1(t)$, monotonically grows as time increases and tends to an asymptotic value dependent on $r_e < r_e^*$.

- (ii) the transient corona structure depends on the diffusivity of all proteins. For the same parameters as in (i), it tends, as diffusivity increases, to the structure of the corona determined by the ODE model. Diffusivity reduces the maximum values of the HSA and Fib concentrations, $u_2(t)$ and $u_3(t)$ but does not affect the steady-state concentrations of all proteins that can be determined by formula (6) after solving simple equation (7).

Despite some shortcomings, we believe that the PDE model and modeling results can be useful in studying the layer of protein covering the surface of nanoparticles.

Acknowledgements We are grateful to Drs. M. Galagudza and A. Myasnikov who drew our attention to the nanoparticle–protein corona formation problem and anonymous reviewers whose valuable suggestions helped to improve this paper.

Compliance with Ethical Standards

Competing interests The authors declare that they have no competing interests.

References

1. Rahman, M., Laurent, S., Tawil, N., Mahmoudi, M.: Protein–Nanoparticle Interaction, vol. 15. Springer, Berlin (2013)
2. Fleisher, C.C., Payne, C.K.: Nanoparticle–cell interactions: molecular structure of the protein corona and cellular outcomes. *Acc. Hem. Res.* **47**, 2651–2659 (2014)
3. Vroman, L., Adams, A.L., Fisher, G.C., Munoz, P.C.: Interaction of high molecular weight kininogen, factor XII, and fibrinogen in plasma at interfaces. *Blood* **55**, 156–159 (1980)
4. Cedervall, T., Lynch, I., Lindman, S., Berggard, T., Thulin, E., Nilson, H., Dawson, K.A., Linse, S.: Understanding the nanoparticle–protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles. *Proc. Natl. Acad. Sci. USA* **104**, 2050–2055 (2007)
5. Jung, S.Y., Lim, S.M., Albertorio, F., Kim, G., Gurau, M.C., Yang, R.D., Holden, M.A., Cremer, P.S.: The Vroman effect: a molecular level description of fibrinogen displacement. *J. Am. Chem. Soc.* **125**, 12782–12786 (2003)
6. Noh, H., Vogler, E.A.: Volumetric interpretation of protein adsorption: competition from mixtures and the Vroman effect. *Biomaterials* **28**, 405–422 (2007)
7. Oberle, M., Yigit, C., Angioletti-Uberti, S., Dzubiella, J., Ballauff, M.: Competitive protein adsorption to soft polymeric layers: binary mixtures and comparison to theory. *J. Phys. Chem. B* **119**, 3250–3258 (2015)
8. Yigit, C., Welsh, N., Ballauff, M., Dzubiella, J.: Protein sorption to charge microgels: characterizing binding isotherms and driving forces. *Langmuir* **28**, 14373–14385 (2012)
9. Lundqvist, M., Stigler, J., Elia, G., Lynch, I., Cedervall, T., Dawson, K.A.: Nanoparticle size and surface properties determine the protein corona with possible implications for biological impacts. *Proc. Natl. Acad. Sci. USA* **105**, 14265–14270 (2008)
10. Lynch, I., Dawson, K.A.: Protein–nanoparticle interactions. *Nano Today* **3**, 40–47 (2008)
11. Lundqvist, M., Stigler, J., Cedervall, T., Berggard, T., Flanagan, M.B., Lynch, I., Elia, G., Dawson, K.: The evolution of the protein corona around nanoparticles: a test study. *ACS Nano* **5**, 7503–7509 (2011)
12. Mahmoudi, M., Lynch, I., Ejtehadi, M.R., Monopoli, M.P., Bombelli, F.B., Laurent, S.: Protein–nanoparticle interactions: opportunities and challenges. *Chem. Rev.* **111**, 5610–5637 (2011)

13. Aggarwal, P., Hall, J.B., McLeland, C.B., Dobrovolskaia, M.A., McNeil, S.E.: Nanoparticle interaction with plasma proteins as it relates to particle biodistribution, biocompatibility and therapeutic efficacy. *Adv. Drug. Deliver. Rev.* **61**, 428–437 (2009)
14. Welsch, N., Lu, Y., Dzubiella, J., Ballauff, M.: Adsorption of proteins to functional polymeric nanoparticles. *Polymer* **54**, 2835–2849 (2013)
15. Dell'Orco, D., Lundqvist, M., Oslakovic, C., Cedervall, T., Linse, S.: Modelling the time evolution of the nanoparticle–protein corona in a body fluid. *PLoS ONE* **5**, 1–8 (2010)
16. Sahneh, F.D., Scoglio, C., Riviere, J.: Dynamics of nanoparticle–protein corona complex formation: analytical results from population balance equations. *PLoS ONE* **8**, 1–10 (2013)
17. Welsch, N., Dzubiella, J., Graeber, A., Ballauff, M.: Protein binding to soft polymer layers: a quantitative study by fluorescence spectroscopy. *Soft Matter* **8**, 12043–12052 (2012)
18. LeDuck, C.A., Vroman, L., Leonard, E.F.: A mathematical model for the Vroman effect. *Ind. Eng. Chem. Res.* **34**, 3488–3495 (1995)
19. Aveyard, R., Haydon, R.: *Introduction to the Principles of Surface Chemistry*. Cambridge University Press, Cambridge (1973)
20. Seelig, J.: Thermodynamics of lipid–peptide interactions. *Biochem. Biophys. Acta* **1666**, 40–50 (2004)
21. McLaughlin, S.: The electrostatic properties of membranes. *Annu. Rev. Biophys. Chem.* **18**, 113–136 (1989)
22. Ygit, C., Heyda, J., Ballauff, M., Dzubiella, J.: Like-charged protein–polyelectrolyte complexation driven by charge patches. *J. Chem. Phys.* **143**, 064905 (2015)
23. Yu, S., Xu, X., Yigit, C., van der Giet, M., Zidek, W., Jankowski, J., Dzubiella, J., Ballauff, M.: Interaction of human serum albumin with short polyelectrolytes: a study by calorimetry and computer simulations. *Soft Matter* **11**, 4630–4639 (2015)
24. Vilaseca, P., Dawson, K.A., Franzese, G.: Understanding and modulating the competitive surface-adsorption of proteins through coarse-grained molecular dynamics simulations. *Soft Matter* **9**, 6978–6985 (2013)
25. Vilanova, O., Mittag, J.J., Kelly, P.M., Milani, S., Dawson, K.A., Radler, J.O., Franzese, G.: Understanding the kinetics of protein–nanoparticle corona formation. *ACS Nano* **10**, 10842–10850 (2016)
26. Samarskii, A.A.: *The Theory of Difference Schemes*. Marcel Dekker, New York (2001)
27. Press, W.H., Teukolsky, S.A., Vetterling, W.T., Flannery, B.P.: *Numerical Recipes: The Art of Scientific Computing*, 3rd edn. Cambridge University Press, Cambridge (2007)
28. Shampine, L.F., Gladwell, I., Thompson, S., Beardah, C.: *Solving ODEs with MATLAB*. Cambridge University Press, Cambridge (2003)
29. Lassen, B., Malmsten, M.: Competitive protein adsorption at plasma polymer surfaces. *J. Colloid Interface Sci.* **186**, 9–16 (1997)