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ABSTRACT

Depletion interactions between colloids of discoidal shape can induce their self-assembly into columnar aggregates. This is an effect of entropic origin with important implications in a range of colloidal systems, particularly in the clustering of erythrocytes that determine the rheological properties of blood. Here, we investigate the equilibrium state reached by discoidal colloids in a solution of smaller depletant particles. We develop a thermodynamic model of depletion-induced aggregation based on self-assembly theory and solve it analytically. We test the validity of the model by using Langevin simulations of a system of discs and depletant particles in which the depletion interaction emerges naturally. In addition, we consider the effect of an attractive interaction between depletant and discoidal particles, which we show induces a re-entrant dependence of aggregation with temperature.

I. INTRODUCTION

Depletion forces are effective interactions of entropic origin ubiquitous in a large variety of colloidal systems. They arise when colloidal particles are immersed in a solution of smaller particles or polymers. To maximize the volume available to the smaller solutes and thus increase the overall entropy of the system, the aggregation of the larger colloids is favored, generating an effective interaction between them.[1–5] Due to their entropic origin, depletion forces are difficult to avoid and often determine the stability of colloidal suspensions in polymer solutions. Depletion interactions can be markedly anisotropic depending on the shape of the interacting colloids. A number of different naturally occurring and custom-made shapes have been shown to self-assemble due to depletion forces into a rich variety of complex structures.[6–10] In fact, the effect of depletion has been proposed as a possible driving force to direct the self-assembly of colloids into pre-designed structures in the quest to synthesize new functional materials.[6,8,9,11,12]

Of special interest are colloidal particles with discoidal geometry, which were shown to be good candidates for the controlled self-assembly of columnar structures with desired properties.[7,9,11,12] In addition, depletion-induced self-assembly might explain the formation of aggregates of red blood cells in blood. Indeed, it has been long known that erythrocytes, with discoidal geometry, aggregate into columnar structures—called rouleaux—when blood is at rest. The formation of rouleaux determines the rheological properties of blood and is the main cause of its marked non-Newtonian flow behavior.[13,14] The driving force of such an aggregation process is still debated between a bridging and a depletion model. On the one hand, the bridging model proposes that the aggregation of red blood cells occurs due to the bridging forces between adjacent cell membranes due to the adsorption of specific proteins. The depletion model, on the other hand, proposes that the formation of rouleaux is caused by the unspecific depletion interaction between red blood cells due to the presence of large concentrations of unspecific depletant macromolecules in blood plasma.[14–16]

The first theoretical account of depletion forces was given by Asakura and Oosawa,[1] and since then the basic properties of the depletion interaction were widely investigated in a variety of

colloidal systems both theoretically[2,5,17,18] and experimentally.[3,4,7] Computer simulations were also used to provide further insight into depletion and to investigate the dependence of depletion forces on distance, depletant concentration, and the geometry of the colloidal particles.[19–21] In addition, there is also a large amount of work devoted to the phenomenological description of the structures generated by depletion in colloidal dispersions.[6,9,11,16,22]

In this article, we propose a simple thermodynamic model to understand the equilibrium state of aggregation of discoidal particles into columnar structures induced by depletion interaction. The model can be solved analytically, providing a complete description of the equilibrium distribution of aggregates formed in terms of the parameters of the problem. To validate the theoretical approach, we perform computer simulations of a system of discs and depletant particles interacting solely through repulsive interactions in which depletion forces between discs emerge naturally. The distribution of the structures formed at equilibrium is in good agreement with the predictions of the model. To investigate the competition between bridging and depletion in our model, we also consider an extra attractive interaction between depletant and discoidal particles, which is shown to cause a re-entrant dependence of aggregation with temperature.

II. THERMODYNAMIC MODEL

The effective depletion interaction potential between two colloidal particles separated by a distance d is, to a good approximation, given by[1,2,23]

$$W(d) = -c_P k_B T V_{ov}(d), \tag{1}$$

where k_B is the Boltzmann constant, T is the temperature, c_P is the concentration of the depletant particles, and $V_{ov}(d)$ is the overlap volume of the regions around the colloidal particles excluded to the presence of depletant. The range of the interaction is given by the size of the depletant particles a, much smaller than the size of the colloidal particles. In the case of disc-shaped particles of radius R_D and width h (with a large aspect ratio $R_D/h \gg 1$ and $R_D/a \gg 1$), the face-to-face interaction between discs dominates over face-to-side or side-to-side interactions, as it is justified theoretically and experimentally verified in Ref. 7. Consequently, we can assume that aggregation occurs in one dimension, along the direction perpendicular to the plane of the discs. To evaluate the face-to-face interaction, it is useful to determine the overlap volume of two parallel identical discs separated a distance d and centers displaced by $r < R_D$, given by

$$V_{ov}(r,d) = \begin{cases} A(r)(a-d), & d < a, \\ 0, & d \geq a, \end{cases}$$

with $A(r) = 2R_D^2 \arccos(r/2R_D) - (r/2)\sqrt{4R_D^2 - r^2}$. Owing to the short range of the depletion interaction, we consider that the total interaction energy of an aggregate of n discs is proportional to the number of contacts (bonds) between the discs, $-(n-1)\varepsilon_0$. The face-to-face effective interaction energy ε_0 is taken as the average of the interaction potential Eq. (1) over its range, which can be written as $\varepsilon_0 = c_P k_B T \pi R_D^2 (a/2) f$. Here, $f \sim 1$ is a dimensionless factor that captures the effect of the edges of the disc and deviations from the perfect parallel face-to-face configurations.[24]

The formation of aggregates at equilibrium induced by the depletion interaction between disc-shaped colloidal particles can be understood using self-assembly theory.[25,26] In this formulation, aggregates with different size are considered as different species, which in equilibrium can reversibly convert into one another. We consider diluted suspensions of disc-shaped colloidal particles in which the interactions between aggregates can be neglected. In this regime, the chemical potential of a disc in an aggregate with n discs is given by[26]

$$\mu_n = \mu^0 + \frac{1}{n}\left[k_B T \ln\left(\frac{\phi_n}{n}\right) - (n-1)\varepsilon_0\right], \tag{2}$$

where $\phi_n = c_n/c_0$ is the concentration of discs in n-disc aggregates over a reference concentration c_0 defined by the size of the constituent particles. The conditions of thermodynamic equilibrium for the different species ($\mu_n = \mu_1, \forall n$) and the conservation of the total disc concentration $\phi_D = \sum_{n=1}^{\infty} \phi_n$ completely define the state of the system.[26–28] From such conditions and using Eq. (2), one obtains the probability $P(n)$ that a given aggregate is composed of n discs,

$$P(n) = y(1-y)^{n-1}. \tag{3}$$

The average number of discs per aggregate is given by

$$\langle n \rangle = \sum_{n}^{\infty} nP(n) = \frac{1}{y}, \tag{4}$$

where

$$y = \frac{1}{2N^{*2}}\left[\sqrt{1 + 4N^{*2}} - 1\right] \tag{5}$$

and

$$N^* \equiv \sqrt{\phi_D e^{\gamma}}, \quad \gamma \equiv c_P \pi R_D^2 f a/2. \tag{6}$$

Note that $P(n)$ is a geometric distribution of a process of n Bernoulli trials with success probability y. The parameter N^*, given by the disc concentration ϕ_D and the disc–disc interaction, completely determines the aggregation state of the solution.[27,28] For a given size of discs and depletant particles, aggregation is much more sensitive to the concentration of depletant, which defines disc–disc interaction than to disc concentration. This is shown in Fig. 1, where the average number of discs per aggregate $\langle n \rangle$ is shown as a function of the concentrations of discs and depletant particles. It is worth noting that even in diluted conditions, long columnar aggregates can be created. Thus, by increasing the average length of the assemblies, one can induce a transition from an isotropic to a nematic phase through a wide region of coexistence between the two phases.[29] Due to the entropic origin of the depletion interaction, the interaction energy of aggregates scales with $k_B T$ [see Eq. (2)]. Consequently, the distribution of aggregates [Eq. (3)] and the average number of

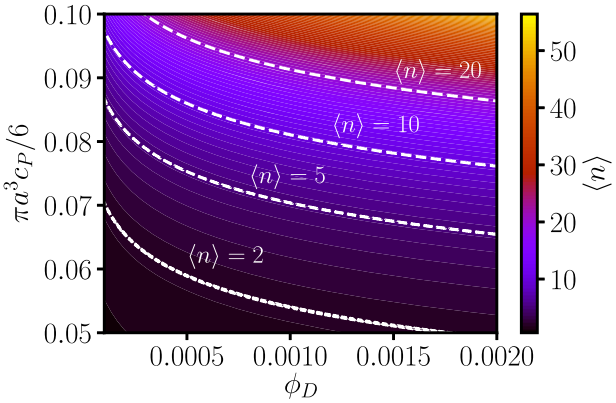

FIG. 1. Average number of discs per aggregate, $\langle n\rangle$, as a function of ϕ_D and c_P for $2R_D/a = 11.67$.

discs per aggregate [Eq. (4)] do not depend on the temperature of the system. In the range of low depletant concentration, depletion agents with different size should act in an additive fashion to induce an effective interaction between discs. Consequently, in a polydisperse depletant solution, the equilibrium distribution of aggregates should be given by Eq. (3) with $\gamma = \pi R_D^2 f/2\sum_i c_P^{(i)} a^{(i)}$, where $c_P^{(i)}, a^{(i)}$ are the concentration and size of depletant type i, respectively.

III. COMPUTER SIMULATIONS

To investigate aggregation due to depletion and bridging interactions, we carried out computer simulations of a system of disc-shaped colloids in a solution of smaller depletant spherical particles in contact with a thermal bath. Each one of the discoidal colloids is modeled as a group of spherical particles arranged in a disc shape, which collectively behave as a rigid body.[30] In this scheme, the dynamics of the disc is solved as a single rigid body with only three translational and three orientational degrees of freedom. The spherical beads forming a disc do not interact with one another, but they interact with spherical beads belonging to other discs and with spherical depletant particles. The interactions among all the spherical beads in the simulation are modeled through a truncated and shifted Lennard-Jones potential

$$U^{(ij)}(r) = \begin{cases} U_{LJ}^{(ij)}(r) - U_{LJ}^{(ij)}(r_c), & r < r_c, \\ 0, & r \geq r_c, \end{cases}$$

where $U_{LJ}^{(ij)}(r) = 4\varepsilon_{ij}\left[(\sigma_{ij}/r)^{12} - (\sigma_{ij}/r)^6\right]$ and r is the distance between particles i and j. Here, ε_{ij}, σ_{ij}, and r_c define the energy, the range, and the cutoff of the interaction, respectively. In the cases considered, we have chosen $\varepsilon_{ij} \equiv \varepsilon = 1$ for all interactions, $\sigma_{11} \equiv \sigma = 1$ for the interaction between disc beads belonging to different discs, $\sigma_{22} = 1.2$ for interactions between depletant particles, and $\sigma_{12} = 1.1$ for interactions between disc and depletant particles following the Lorentz–Bertheloz rule. To investigate the emergence of the depletion interaction and test the theoretical model for depletion aggregation, we consider only repulsive interactions between the beads by setting the cutoff distance to $r_c = \sigma_{ij}2^{1/6}$ [Weeks–Chandler–Anderson (WCA) model[31]].

To investigate the competition between bridging and depletion, we also consider an extra attractive interaction between depletant and discoidal particles. To this end, the interactions between the beads forming the disc particles and the spherical depletant particles are described through a truncated and shifted Lennard-Jones potential with $\tilde{\varepsilon}$, $\tilde{\sigma}_{12} = 1.1$, and a cutoff radius $r_c = 2\tilde{\sigma}_{12}$. In contrast to the WCA model, in this case, the interaction between disk beads and depletant particles contains an attractive region of range $\tilde{\sigma}_{12}$ characterized by the energy $\tilde{\varepsilon}$.

We report results obtained by considering systems with $N = 512$ discoids (each one composed of 106 beads), although we have also performed simulations with 1000 discoids to check for finite size effects. The system is prepared in a random configuration at given concentrations of discs ϕ_D and depletant c_P. Periodic boundary conditions are applied in the three spatial dimensions. The dynamics of discs and depletant particles is then solved by integrating numerically the Langevin stochastic equations of motion with fixed volume, temperatur,e and number of particles. The number of integration steps of the simulation depends on the time the system takes to attain equilibrium, ranging from 10^7 to 5×10^8 steps depending on the conditions considered. The temperature of the system is set to $k_B T = 1$ unless stated otherwise and the time step used is $dt = 0.002$ in the reduced units defined by ε and σ. All simulations were performed using the simulation package HOOMD-blue 2.2.3[32,33] running on Tesla P100 GPUs.

IV. RESULTS AND DISCUSSION

A. Pure depletion aggregation

First, we investigate the aggregation of discs in simulations with purely WCA repulsive interactions. The formation of aggregates is observed at high enough concentrations of discs and depletant due to the naturally emerging depletion interaction. In Fig. 2, we show

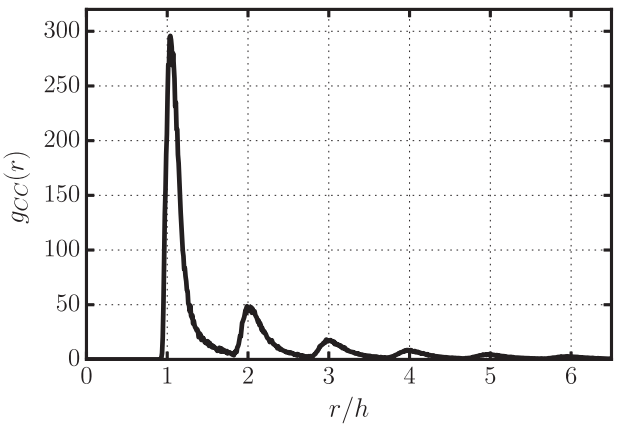

FIG. 2. Radial distribution function of the centers of the discoids $g_{CC}(r)$ as a function of distance in units of the thickness of a disc h for a system of discs of radius $R_D = 5$, $c_P = 0.14$, and $\phi_D = 0.078$.

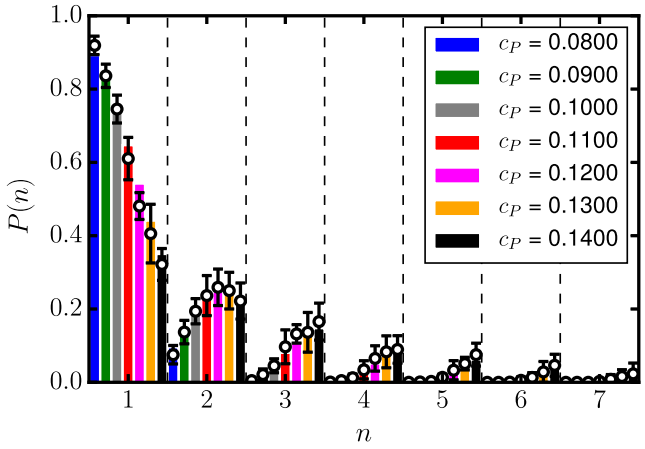

FIG. 3. Frequency of occurrence $P(n)$ vs aggregate size n. Symbols with error bars represent results obtained from Langevin simulations. Bins correspond to the predictions of the theoretical model. In all cases, the same value $f = 1.3$ is used. Symbols and bins are color coded to identify different depletant concentrations.

the radial distribution function (RDF) of the centers of the discoids of a typical simulation in which aggregates are formed. The RDF exhibits a very prominent peak at $r = h$ and subsequent peaks of decaying height at distances multiples of h, evidencing a columnar structure of the aggregates due to the pre-eminence for face-to-face over face-to-side or side-to-side interactions between the discoidal particles. The lack of face-to-side and side-to-side arrangements observed in simulation is consistent with the smaller volume reduction to the presence of depletants induced by face-to-side, ΔV_{fs}, and side-to-side, ΔV_{ss}, with respect to the volume reduction of face-to-face, ΔV_{ff} configurations. Such reductions are estimated to be $\Delta V_{fs} \simeq 0.06\Delta V_{ff}$ and $\Delta V_{ss} \simeq 0.03\Delta V_{ff}$.

To characterize the formation of aggregates and compare the results from simulations with the predictions of the theoretical model, we calculate from the trajectories of the simulations the frequency of occurrence of a size n aggregate, $f(n,t)$, and the average number of discs per aggregate, $\bar{n}(t)$, as a function of simulation time. We consider that two discs belong to the same cluster when they are within distances equivalent to the first minimum of the disc–disc radial distribution function (RDF). When the system reaches thermodynamic equilibrium, $f(n,t)$ and $\bar{n}(t)$ exhibit a stationary behavior [see the inset in Fig. 4(a)] and averaged quantities are collected to obtain the equilibrium quantities $P(n)$ and $\langle n \rangle$.

First, we investigate the dependence of aggregate formation on the disc–disc depletion interaction by varying the concentration c_P of depletant particles in the system. In Fig. 3, we show the equilibrium distribution of aggregates formed at different depletant concentrations for discs of radius $R_D = 5$ at a concentration $\phi_D = 0.001$. In all cases, we obtain a distribution in very good agreement with the geometric distribution predicted by the thermodynamic model. The corresponding average aggregate size in equilibrium $\langle n \rangle$ is shown in Fig. 4(a) as a function of depletant concentration c_P. The results obtained from simulations exhibit a rapid increase with c_P, in good agreement with Eq. (4). Only at the highest value of depletant concentration there is a significant deviation from theoretical predictions, which can be attributed to the departure from the dilute regime assumed in Eq. (2).

The formation of columnar aggregates also depends on the size of the discs, as captured by γ in Eq. (6). In Fig. 4(b), the dependence of $\langle n \rangle$ on the discs radius is shown for given concentrations of discs and depletant particles. The results from simulations follow the theoretical trend except for the larger disc considered, for which aggregation is lower than predicted. The volume fraction occupied by discs increases quadratically with their radius, reaching values ($\sim$0.14) for which mutual interactions between discs should be considered. Due to the contribution to the chemical potential from the entropy of aggregates, the equilibrium distribution of aggregates not only depends on the effective depletion interaction between discs but also on the concentration of discs in solution. Indeed, the average number of discs per aggregate is $\langle n \rangle \sim \sqrt{\phi_D}$, as shown in Fig. 4(c) for simulations, and consistent with the theoretical result [Eq. (4)].

We check that in the conditions investigated in our simulations, the columnar aggregates are in the isotropic phase and

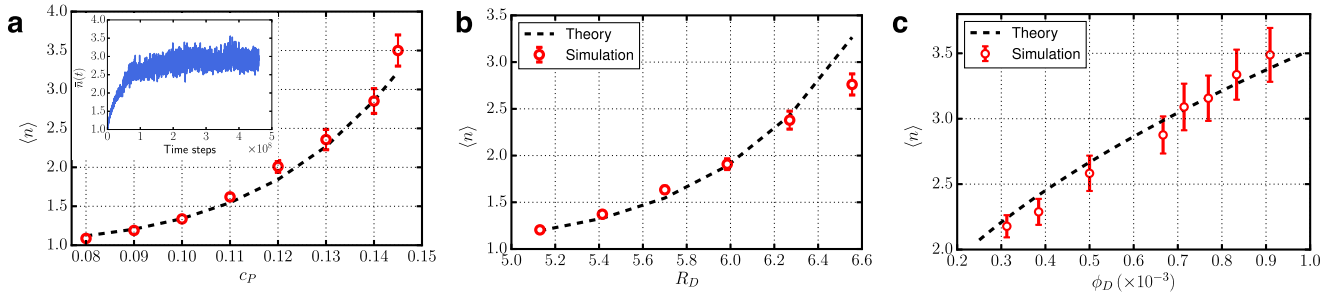

FIG. 4. (a) Average number of discs per aggregate as a function of depletant concentration for discs of radius $R_D = 5$ at a concentration $\phi_D = 0.001$. Inset: average number of discs per aggregate as a function of simulation time. (b) Average number of discs per aggregate as a function of the radius of the disc for $c_P = 0.11$ and $\phi_D = 0.001$. (c) Average number of discs per aggregate as a function of the disc concentration ϕ_D for discs of radius $R_D = 5$ and $c_P = 0.14$. In all cases, symbols with error bars represent results from Langevin simulations, and the dashed line corresponds to the prediction of the theoretical model. In all cases, the same value $f = 1.3$ is used.

exhibit no preferred orientation, as shown by the orientational order parameter

$$S = \frac{1}{2}\langle 3\cos^2\theta - 1\rangle, \tag{7}$$

which is statistically negligible for all the cases considered. Here, θ is the angle between an arbitrary fixed axis and the direction defined by the plane of the discs, and ⟨⟩ denotes the average over all the discs and simulation frames considered. We also verify that the aggregate distribution is independent of temperature by performing simulations at a given set of parameters R_D, c_P, ϕ_D, and k_BT = 0.5, 1, 2 (not shown).

The systems investigated in our numerical simulations to test the theoretical model are limited to low aggregation values. The reason is two-fold. First, the simulated system consists of a large number of particles since the depletant is considered explicitly. In addition, long simulations are required to reach the equilibrium state ($\simeq 10^8$ simulation steps in representative simulations). As a consequence, computational limitations restrict the size of the systems that we can consider in our simulations to cases with 512 discs. Second, equilibrium distributions are monotonic slowly decaying functions of the cluster size [see Eq. (3) and Fig. 3], and to be able to properly describe the equilibrium state, numerical simulations must be capable to account for the whole distribution.

The theoretical model introduced to describe the equilibrium aggregation state induced by depletion interactions has two main limitations. First, the expression for the chemical potential [Eq. (2)] is valid for diluted systems. In fact, in our simulations, we observe deviations from the theoretical predictions of the model for volume fractions of discs and depletant $\gtrsim 0.13$. The second limitation concerns the assumption that face-to-face interactions are dominant over face-to-side and side-to-side interactions. While face-to-side are always smaller than face-to-face interactions,[7] long clusters can have side-to-side interactions comparable or even larger than face-to-face interactions. We can estimate the cluster threshold size n_{th}, which determines the dominance of side-to-side over face-to-face interactions, given by[7] $n_{th} \simeq R_D^{3/2}/(ha^{1/2})$. For cases with a significant probability of containing aggregates of size $n \gtrsim n_{th}$, side-to-side arrangements cannot be neglected and our theoretical model is not applicable. For the disc and depletant sizes considered in our numerical simulations, $n_{th} \simeq 14$, well beyond the maximum cluster size with a significant probability of occurrence (see Fig. 3).

B. Competition between bridging and depletion aggregation

To understand the interplay between the bridging and depletion mechanisms of cluster formation in, e.g., blood,[14] we have considered the case in which an extra attractive interaction, characterized by the energy $\tilde{\varepsilon}$, exists between discs and depletant particles. Such interaction should promote the formation of columnar assemblies of discs mediated by depletant particles, structures that are expected to form at low temperatures. We have performed Langevin simulations of this model and characterized the aggregation as a function of temperature. Figure 5 shows the dependence of the mean aggregate size $\langle n\rangle$ on temperature, which exhibits re-entrance. Both at high and low temperatures, we observe self-assembly of discs into clusters, with a suppression of aggregation

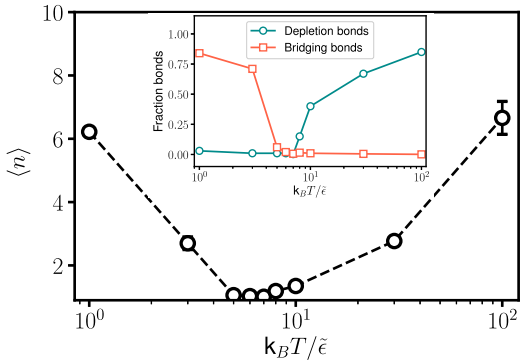

FIG. 5. Average number of discs per aggregate as a function of temperature for a model with an attractive interaction between discs and depletant particles. In this case, discs have a radius $R_D = 5$, $a = 1.5$, $c_P = 0.12$, and $\phi_D = 0.001$. Inset: fraction of the total number of possible bonds formed by bridging (bridging bonds) and depletion (depletion bonds) for different temperatures.

at intermediate values of the temperature. Although in all cases aggregates are linear, the mechanism and structure of aggregation differs with temperature. While at $k_BT \lesssim \tilde{\varepsilon}$, discs within columnar structures are connected by depletant particles (bridging bonds), at $k_BT \gg \tilde{\varepsilon}$, the depletant–disc attractive interaction is irrelevant and it is the depletion interaction that binds discs in contact with one another within the linear cluster (depletion bond). In the inset of Fig. 5 we represent the fraction of the total number of possible bonds between discs formed by bridging or depletion as a function of temperature.[34] At low temperatures ($k_BT/\tilde{\varepsilon} < 6$), aggregates are formed exclusively through bridging by depletant particles. In contrast, for high temperatures ($k_BT/\tilde{\varepsilon} > 8$), columnar clusters consist of discs bound by depletion bonds. There seems to be no range of temperatures where there is a coexistence of the two types of bond, indicating that both mechanisms are mutually exclusive.

V. CONCLUSIONS

In this article, we have investigated the aggregation into columnar structures of colloidal disc-shaped particles in a solution of smaller spherical particles. First, we consider a case in which the particles interact solely through repulsive interactions, and the aggregation of the discs is caused by entropy-driven depletion interactions. For this case, we introduce a thermodynamic model based on self-assembly theory,[26] which allows us to predict the equilibrium distribution of aggregates generated by depletion interaction. We demonstrate that the aggregation state depends on the parameters of the colloidal solution through the dimensionless number $N^* \equiv \sqrt{\phi_D e^{\gamma}}$, with $\gamma \equiv c_P \pi R_D^2 f a/2$ (R_D, ϕ_D are the radius and concentration of discs; and a, c_P are the radius and concentration of depletants). These results are shown to be in good agreement with computer simulations of a model of discs and depletant particles that interact only through repulsive interactions and where depletion forces emerge naturally. Second, we have used computer simulations to investigate the competition between bridging and depletion-induced aggregation in a model of discs and spherical

particles with an additional short range attractive interaction. We find that the formation of disc aggregates exhibits a re-entrant dependence on temperature. While at low temperatures, linear clusters are formed by discs connected by spherical particles (bridging), at high temperatures, the formation of columnar aggregates is due to depletion interaction, which binds discs in contact to one another. Interestingly, we find that there is no cluster formation at intermediate temperatures and no coexistence of the two types of aggregation mechanisms at any temperature, suggesting that both are mutually exclusive.

The theoretical predictions for the cluster size distribution can be exploited to analyze the relevance of depletion-induced self-assembly on the origin of red blood cell aggregates.[14–16] Although in physiological conditions depletion-induced aggregation of red blood cells should be too strong to attain equilibrium ($\gamma \approx 10^3$), one can prepare red blood cell suspensions in highly diluted plasmas to investigate the equilibrium aggregation state (dilutions of 1% in protein-free isotonic buffers, routinely realized in experiment, should suffice). The dependence of the assemblies on the size and concentration of proteins and the temperature should provide valid tests to discriminate depletion forces from other sources of aggregation.

The thermodynamic model developed in this article can be extended to describe the formation of aggregates by depletion forces between colloidal particles with other geometries. Indeed, the short range of the depletion interaction allows for a decomposition of the aggregate energy in terms of the number of contacts with other colloids. For example, the clustering of long rod-like particles due to the presence of depletant[6,22] could be treated using a similar approach, provided that the aggregation occurs in this case in the plane perpendicular to axis of the rod.

Due to its entropic origin, depletion-induced aggregation is independent of temperature. Hence, if colloids (of any geometry) and depletant particles interact through additional attractive forces, the competition between these two interactions should lead to a re-entrant thermal behavior in their equilibrium self-assembly, as shown here for the case of discoidal colloids. While at low temperatures, clustering is mediated by the depletant particles (bridging bonds), at high temperatures, aggregation occurs by direct contact of colloidal particles due to the unbalanced pressure from the depletant.

AUTHORS' CONTRIBUTIONS

C.C. designed the study, performed some of the calculations, and co-wrote the manuscript. M.D.-M. performed some of the calculations. I.P. helped design the study and co-wrote the manuscript.

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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