Phase diagram of two-patch colloids with competing anisotropic and isotropic interactions

Isha Malhotra and Sujin B Babu

Out of Equilibrium Group, Department of physics, Indian Institute of Technology, Delhi-110016, India

E-mail: sujin@physics.itd.ac.in

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Abstract

Patchy particles are considered to be a good model for protein aggregation. We propose a novel method to generate different structures of glucose isomerase protein such as chains, crystals and bundles by utilising aggregation of two-patch colloidal particles in presence of competing isotropic and anisotropic potential. We calculate the equilibrium phase diagram of two-patch colloidal particles and demonstrates the coexistence of different phases like disordered clusters, chains, crystals and bundles depending on the relative strength of isotropic and anisotropic potential. We also show that the formation of network of bundles is metastable against the formation of thermodynamically favored finite sized bundles along with thermodynamically stable crystals. These bundles appear to be helical in structure similar to that observed in sickle cell hemoglobin. The simulation results show that the method can characterize phase behaviour of glucose isomerase protein, which provides a novel tool to unveil self-assembly mechanism of protein under different conditions.

Keywords: anisotropic interactions, phase diagram, self assembly, phase separation, bundles, crystals

Supplementary material for this article is available online

(Some figures may appear in colour only in the online journal)

1. Introduction

Human diseases such as cataract, sickle cell anaemia, Alzheimer’s disease, amyotrophic lateral sclerosis are caused due to unwanted protein aggregation [1–4]. However, it is also essential to build protein crystals via self assembly to obtain insights into the structure of proteins for various pharmaceutical applications including targeted drug delivery [5, 6]. Therefore, studying the formation of protein aggregates is vital. Protein aggregation has been studied by utilising patchy particles [7–11], Kern and Frenkel [12] patchy particle model has been shown to mimic certain type of equilibrium protein crystals [13]. Later patchy particles along with isotropic interaction [14–18] were found to be closer to experiments. Whitelam [19] proposed a 2D model where he showed that different pathways for crystallization are possible by tuning the relative strength of the nonspecific and specific interactions. It was shown that by playing with the number of patches along with short range isotropic interaction reproduces the liquid–liquid coexistence curves of gamma-crystalline and lysozyme proteins [16]. Audus et al [20] also studied the phase behaviour for five patch particle with competing isotropic and anisotropic interaction, where they observed only liquid–liquid phase separation. Chain to bundle transition as observed for lysozyme protein [21] is mimicked by a two patch particle where irreversible patchy interaction is coupled with reversible isotropic interaction [22]. Malhotra et al [23] further studied how the formation of these bundles can be accelerated and inhibited using different types of obstacles. Huisman et al [24] also observed the formation of bundles and they showed that the transition is similar to sublimation transition of polymers.
Preisler et al [25] also observed the formation of a metastable tubes for the case of particles with a single patch.

In the present work, our aim is to utilise the patchy particles to mimic the structures of glucose isomerase protein such as nanorods (chains), bundles and crystals and to predict the equilibrium phase diagram. In order to achieve this we model the aggregation of two-patch colloidal particles under competing anisotropic and isotropic potentials using patchy Brownian cluster dynamics (PBCD) [22, 23, 26]. PBCD has already been utilised to study step growth polymerization by Prabhu et al, they utilised this algorithm to produce the correct static and dynamic properties of a single polymer chain [26]. BCD has been used to simulate hard spheres interacting through a square well potential. It has been shown that structure of the equilibrium states and value of self diffusion coefficients matched with that of EDBD (event driven Brownian dynamics) [27, 28]. Besides mimicking the structures that are observed for glucose isomerase protein, we are able to observe the existence of rich phases such as chains/crystals, thermodynamically favored bundles/crystals, disordered clusters/crystals and disordered clusters by tuning both anisotropic and isotropic interactions. For two patch particles, Li et al [29] observed the formation of different stable crystal structures when the patch well depth was kept twice of isotropic well depth. But unlike Li et al, we have observed the chain to bundle transition.

This paper is arranged in the following way. In section 2, we introduce our model and simulation technique and explain how we implement the interaction between particles. In section 3, the results of our simulations are discussed. We show the formation of different structures starting from random distribution of particles and we discuss how the equilibrium phase diagram has been predicted. In section 4, main findings of our work are concluded.

2. Model and simulation technique

In the present study, we randomly distribute \( N \) spheres each of diameter \( \sigma \) in a cubic box of edge length \( L = 50 \) with periodic boundary condition. We have employed the potential developed by Kern and Frenkel to simulate inter-particle anisotropic interactions [12]. We couple isotropic and anisotropic potential, hence total potential \( U(\mathbf{r}_{ij}, \mathbf{v}_i, \mathbf{v}_j) \) is given by:

\[
U(\mathbf{r}_{ij}, \mathbf{v}_i, \mathbf{v}_j) = \begin{cases} 
\infty & r_{ij} < \sigma \\
-(u_t + u_a) \sigma & \sigma < r_{ij} < \sigma(1 + \epsilon) \\
0 & r_{ij} > \sigma(1 + \epsilon)
\end{cases}
\]

where \( r_{ij} \) is the distance of centre of mass of the \( i \)th particle to the \( j \)th particle and \( \epsilon \) is the interaction range. \( u_t \) and \( u_a \) are the depths of square well for isotropic and anisotropic interactions respectively. \( u_t \neq 0 \) only if \( \mathbf{r}_{ij} \cdot \mathbf{v}_i > \cos \omega \) and \( \mathbf{r}_{ij} \cdot \mathbf{v}_j > \cos \omega \), where \( \omega \) is the semi solid angle of a cone having vertex at the center of a sphere which defines the patch size. In the present work we have used \( \sigma = 1, \, \epsilon = 0.1 \) and \( \omega = 22.5^\circ \), which ensures that only one bond per patch is possible [22, 23]. The single bond per patch condition depends on the patch angular width \( \omega \) and square well interaction range \( \epsilon \). For single bond per patch the maximum opening angle \( \omega_{\text{max}} \) must satisfy the condition \( \sin(\omega_{\text{max}}) \leq \frac{1}{2(1 + \epsilon)} \) [30]. By putting \( \sigma = 1 \) and \( \epsilon = 0.1 \), \( \omega_{\text{max}} \) comes out to be 27.035° and hence we selected 22.5° as our patch size. All quantities are reported in reduced units, hence bond strength is measured in units of \( u / k_B T \) where \( k_B T = 1 \). Reduced time is given by \( t/t_0 \), where \( t_0 \) is the time taken by a particle to travel its own diameter [22] and the volume fraction is defined as \( \phi = (\pi/6)N\text{vol}/L^3 \). We have kept \( \phi = 0.02 \) which corresponds to a total number of \( N_{\text{tot}} = 4774 \) particles. In patchy Brownian cluster dynamics, each simulation step is divided into two steps; movement and cluster construction step. In movement step, we randomly select \( 2N \) times a particle which is either rotated with a step size \( \theta_k \) or translated with a step size \( \xi_T \). In this way, every particle undergoes translational and rotational diffusion in an uncorrelated and independent manner in every step. To fix the value of step sizes, we evaluated the diffusion coefficients of single polymer chains. For an ideal polymer chain of \( m \) monomers, diffusion coefficient is given by \( D = \frac{2}{m} \) [26]. We selected a step size such that it gives a maximum error within 10% of the correct values of diffusion coefficients. In the present study, we have fixed \( \xi_T = 0.013 \) and \( \theta_k = 0.018 \) to ensure the correct diffusional behaviour. All movement steps which lead to the overlap of spheres or breakage of bonds are rejected. The cumulative effect of this movement step is the diffusion of center of mass of clusters. In cluster construction step, when two monomers are in interaction range and their patches are facing each other then a patchy (\( P \)) bond is formed with probability \( \alpha \) and if a bond already exists it is broken with a probability \( \beta \), such that \( \frac{\alpha}{\alpha + \beta} = 1 - \exp(-u_t) \), see figure 1(a). The collection of only these patchy bonded spheres is referred as \( P \)-type cluster. When particles are in interaction range and the patches are not facing each other as shown in figure 1(b), they form non patchy isotropic (NPI) bond with a probability \( \frac{\alpha}{\alpha + \beta} = 1 - \exp(-u_a) \) [26], where \( \alpha_t \) and \( \beta_t \) are the probabilities to form and break the isotropic bond respectively. The collection of these NPI bonded particles is referred as NPI cluster. In this work, we have kept bond forming probabilities \( \alpha_t \) and \( \alpha_a \) as unity. We have considered \( u_t \) ranging from 0 to 2.6 and \( u_a \) values ranging from 0 to 10.

3. Results and discussions

The phase diagram for two-patch model has been shown in figure 2, where we observe the existence of five different phases. At intermediate to high isotropic (1.39 < \( u_t < 2.57 \)) interaction and at low to intermediate anisotropic interactions
interaction ($2 < u_a < 6.67$) strength, we observe the formation of crystals and DC (disordered clusters) as shown in snapshot of the system in figure 3(a). These crystals have fcc/hcp, bcc structures as calculated by bond order orientational parameter (see supplementary information S1 for calculations) (http://stacks.iop.org/JPCM/32/355101/mmedia). As it can be observed, this region of phase diagram is dominated by isotropic part of the potential and the phase separation is similar to what is observed for system having only isotropic potential [27]. For the well width $\varepsilon = 0.1$, the isotropic square well system phase separates at $u_i \geq 2.57$ [27] while in presence of anisotropic interaction, phase separation shifts to $u_i < 2.57$. Below this region, as we decrease $u_i$ and $u_a$, we observe the formation of only DC as shown in figure 3(b). In this region both the isotropic as well as anisotropic part of the potential are relatively small. When $u_a$ is increased ($u_a > 7.69$) keeping the same $u_i = 1.3$, we observe the formation of DC as well as chains, see figure 3(c). This region is dominated by anisotropic part of the potential as $u_a > u_i$. As mentioned before, due to the small patch size only one bond per patch is possible and as anisotropic bond strength is large, it leads to the formation of chains. Due to the presence of a weak isotropic interaction in this region, we also observe a small fraction of DC. When we increase $u_i$ for the same $u_a > 7.69$, we observe the formation of crystals along with chains as isotropic part of the potential is playing a competing role (upto $u_i = 2.14$) as shown in figure 3(d). As $u_i$ is further increased ($u_i > 2.14$), crystals and bundles along with DC are observed as shown in figure 3(e). We also observe that the finite bundle that is formed always has helical arrangement. It has already been shown that a bundle with a helical arrangement is a thermodynamically favored state [31–33], which is probably why we are observing the bundles with crystals [34–37]. For the case of single patch particles, it has been reported that the finite bundles have a lower free energy compared to the lamellar structure which is the equilibrium structure [25].

In order to understand the kinetics of formation of different phases, we follow the average number of neighbors bonded via only isotropic interaction $\langle Z_{NPI} \rangle$ and only patchy interaction $\langle Z_P \rangle$ (in the inset) as a function of reduced time starting from random distribution of particles. For $u_i = 1.39$ and $u_a = 3.33$, we observe only disordered clusters where $\langle Z_P \rangle$ and $\langle Z_{NPI} \rangle$ increases very slowly and equilibrates around a value $10^{-1}$ as the isotropic and anisotropic potential are small. For chains/DC ($Z_P$) $\sim 2$, showing that all the patches are bonded due to high anisotropic interaction strength ($u_a = 10$) and $\langle Z_{NPI} \rangle$ equilibrates around 0.17 due to low isotropic interaction strength ($u_i = 1.39$). When $u_i = 2.3$ and $u_a = 5$, we observe the formation of crystals as seen by the sudden upturn in the average number of neighbors $\langle Z_{NPI} \rangle$, which is also observed in the case of $\langle Z_P \rangle$. When the anisotropic part of the potential is increased ($u_a = 10$), we also observe that $\langle Z_{NPI} \rangle$ increases and a sudden upturn is observed similar to crystal structure.
formation, but \( \langle Z_p \rangle \sim 2 \) indicates that we are having chain like structure. A visual inspection of the images as shown in figure 4, we observe a network made up of bundles similar to that seen in actin filaments \([38]\). Table 1 shows the value of average number of neighbors (\( \langle Z_p \rangle \) and \( \langle Z_{NPI} \rangle \)) of different structures observed in our system.

Colloids with short range interaction phase separates into crystal-gas phase and this transition is first order in nature \([27]\). Starting from random distribution of particles, system may get stuck in a metastable state. In order to know the equilibrium states at different points \((u_a, u_b)\) on the phase diagram, we have taken the system from a random configuration to \((u_a, u_b)\) as well as dissolved an already phase separated system (crystallized) configuration to the same point in the phase diagram \([25, 27]\). Recently, Oh et al \([39]\) have utilised this method to calculate the phase diagram of colloidal particles. In their study, they built each superstructure at a low temperature and gradually increased the temperature to obtain the melting point of each phase. If the dense phase of the phase separated system (crystal phase) dissolves and meets the average number of neighbors (\( \langle Z_{NPI} \rangle \) and \( \langle Z_p \rangle \)) starting from random distribution of particles, then system formed is in equilibrium. Whereas if dense phase does not dissolve and keeps on growing, indicated by increasing value of average number of neighbors shows that the system formed from random distribution of particles is metastable.

In figure 5(a), we have plotted \( \langle Z_p \rangle \) as a function of reduced time, the squares indicate the evolution of system to (3.33, 1.39) (state points are indicated in figure 2) starting from an already phase separated system formed at (5, 2.14) (see snapshot to the left of figure 5) and triangles indicate the evolution to (3.33, 1.39) starting from a random configuration of patchy particles. We observe that the dense crystal phase (indicated by squares) dissolves completely and meets with the curve starting from a random distribution indicating that the DC formed is the equilibrium phase (see snapshot in the right side of figure 5(a)). We also observe that similar trend is observed in the case of \( \langle Z_{NPI} \rangle \) as shown in the inset of figure 5(a) (see video V1 in supplementary information). In figure 5(b), squares indicate the evolution of system to (3.33, 2.14) starting from a phase separated system formed at (5, 2.14) and triangles indicate the evolution of \( \langle Z_p \rangle \) to (3.33, 2.14) starting from a random distribution of particles. We observe that the dense phase initially evaporates indicated by drop in \( \langle Z_p \rangle \) value, but crystal grows again indicating that system formed is metastable in nature (see snapshot to the right top of figure 5(b)). In the inset we can observe that \( \langle Z_{NPI} \rangle \) of the dense phase increases continuously indicating that the crystals are not dissolving in this particular case. When we start the simulation from a random configuration and quench the system to (3.33, 2.14), the system is stuck in a metastable state and we observe only DC (see snapshot to the right bottom of figure 5(b)). From a randomly distributed system when we quench the system to (10, 2.14) which is in the crystal/bundle region of the phase diagram, we observe a network of bundles (see snapshot in figure 4). When we start from an already phase separated system formed in the crystal/DC region (5, 2.14), we observe that the crystals in the system do not dissolve, whereas the DC aggregate together to form finite helical bundles as shown in figure 3(e) (also see video V2 in supplementary information).

To characterize these bundles, we have calculated the average radius of the helix. For two positions of the center of mass \( r_i \) and \( r_{i+1} \) of adjacent monomers that are part of chain which is forming bundle, we define unit tangent vector to the path along the chain \( \hat{T}_i \).

\[
\hat{T}_i = \frac{(r_{i+1} - r_i)}{\Delta \text{dis}_i}, \quad \text{where} \ \Delta \text{dis}_i = |r_{i+1} - r_i| \quad (2)
\]

We then calculate the unit normal vector \( \hat{N}_i \).

\[
\hat{N}_i = \frac{(\hat{T}_{i+1} - \hat{T}_i)}{|\hat{T}_{i+1} - \hat{T}_i|} \quad (3)
\]

\[
\hat{N}_{i+1} \cdot \hat{N}_i = \cos(\Delta \theta_{hel}) \quad \text{where} \ \Delta \theta_{hel} = K_{hel} \Delta \text{dis}_i \quad (4)
\]

\[
\hat{N}_{i+1} \cdot \hat{T}_i = -K_{hel} R \sin(\Delta \theta_{hel}) \quad (5)
\]

where \( K_{hel} = 2\pi/l, l \) is defined as the arc length of one full helical turn. We substitute the value of \( \Delta \text{dis}_i \) and \( \Delta \theta_{hel} \) in equation (4) to calculate the value of \( K_{hel} \). \( R \) is defined as the radius of helix and we evaluate it using equation (5). We have

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**Table 1.** Values of average number of neighbors (\( Z_p \) and \( Z_{NPI} \)) for different structures.

| Structure | \( \langle Z_p \rangle \) | \( \langle Z_{NPI} \rangle \) |
|-----------|-------------------|-----------------|
| Chains    | 2                 | <0.225          |
| Crystals  | \( \approx 1 \)    | >4              |
| DC        | <0.225            | <0.225          |
| Bundles   | 2                 | >4              |

*Figure 5.* (a) \( \langle Z_p \rangle \) is plotted with respect to reduced time at \( u_1 = 1.39 \) and \( u_b = 3.33 \) and inset shows the evolution of \( Z_{NPI} \). (b) \( \langle Z_p \rangle \) is plotted at \( u_1 = 2.14 \) and \( u_b = 3.33 \) and inset shows the evolution of \( Z_{NPI} \). Triangles indicate the evolution of the system starting from random distribution of particles and squares indicate the evolution starting from a phase separated system formed at \( u_1 = 2.14 \) and \( u_b = 5.0 \).
done this calculation for all the chains that are part of bundle and take an average. We have calculated it for 40 such chains and average radius $R_{av}$ is coming out to be $0.62 \pm 0.1$. This calculation indicates that the bundles formed in our system are helical.

To evaluate the coexistence of different phases, we have evaluated free energies of different phases by utilising the methodology as described by Priesler et al [25] (for details of calculations, see supplementary material). We found that the free energy of thermodynamically stable crystal is comparable to that of chains and DC in region of coexistence of chains, crystals and DC. The free energy of finite sized helical bundles is comparable to that of crystals in region of coexistence. The free energy of DC and crystals is comparable in region of coexistence of crystal and DC.

To differentiate between different structures we plot $g(\theta)$ in figure 6, which gives the probability of occurrence of angle $\theta$ between patch vectors of adjacent particles [22, 40–42]. In figure 6(a), we have plotted $g(\theta)$ for the crystal structure and for the DC cluster as obtained from the simulations, also shown in figure. For the case of disordered cluster, we observe that all the angles are possible and hence these clusters are called as disordered cluster. We have isolated the crystals from the phase separated system and then calculated $g(\theta)$ for the crystals alone. We observe 2 prominent peaks for the crystal at $20^\circ$ and $160^\circ$, which indicates that the constituent spheres of the crystal are aligned along the patch vector. Along with this intermediate angles are also possible with much lower probability which may be due to the chains along the surface of the crystal. In figure 6(b), we have plotted $g(\theta)$ after isolating the bundles and chains from a phase separated system (corresponding images are shown in figure). In this case the anisotropic interaction $u_i = 10$ is greater than isotropic interaction $u_i = 1.4$ and we observe chain formation. When the isotropic interaction is higher $u_i = 2.3$ we observe the formation of bundles. The two peaks we observe are consistent with the fact that for a chain as well as a bundle the patch vector of the spheres is aligned either parallel or anti parallel with the neighboring sphere. It is already shown that once the system forms bundles it will twist into a helical structure and this is considered to be a thermodynamically favored state [31, 32]. Qualitatively similar kind of structures are observed in biological systems like sickle cells [33] and actin filaments [38]. Due to the finite twist as predicted by Turner et al [33] and inter-chain bonding, we observe small tails in the distribution of $g(\theta)$ at $40^\circ$ and $130^\circ$ as shown by filled arrows in figure 6(b). Due to the presence of this tail in $g(\theta)$ we can easily differentiate between a bundle and a chain apart from the visual confirmation.

The kinetics of formation of helical bundles in our system is distinct from the formation of helices as proposed in earlier works. Zou et al [43] generated different kinds of supracolloidal helices by modifying the softness of Janus particles. These helical structures are formed by fusion of small and unstable micellar structures. Priesler et al [25] also observed the formation of tubes with single patch particles. They showed that the formation of tubes is metastable against the formation of lamellae structure. Chen et al [44] proposed the formation of helical bundles by step by step addition of individual particles forming small clusters which later fuse together into fibrillar triple helices of finite diameter. Patchy model without isotropic interactions has also been utilised to study the phase behaviour of Lysozyme dispersion [45]. In their model, an additional repulsive part is considered in the potential to account for effective charges on the surface of protein. They have shown that the experimental data are recovered with the correct reduced second virial coefficient only when anisotropic pair interactions are considered on the surface of lysozyme protein.

4. Conclusions

In the earlier work [22], we have studied the aggregation of irreversible patches coupled with reversible isotropic interaction and we found the formation of network of bundles, chains and network like structures. In the present work, we have evaluated the phase diagram of patchy colloidal particles undergoing reversible anisotropic and isotropic interactions. Experimentally, glucose isomerase polymorphs are studied in presence of ammonium sulfate and polyethylene glycol (PEG) [46]. High concentrations of ammonium sulfate (AS) induce a strong anisotropic interaction between glucose isomerase protein. High concentrations of PEG induce a strong isotropic depletion attraction that promotes aggregation. We have shown that the structures observed for glucose isomerase protein [46] can be mimicked by two patch colloidal particle system by
tuning $u_a$ and $u_b$. We conclude that the network of bundles formed at relatively high isotropic and anisotropic interaction strength is meta-stable against the formation of thermodynamically favored finite sized bundles with thermodynamically stable crystals. The bundles which we observe seem to be helical in structure which is a thermodynamically favored state as reported by Grason et al [31, 32]. Similar bundle formation is also observed in the case of sickle hemoglobin fibres [33]. Besides mimicking the structures that have been observed for glucose isomerase protein, we are also predicting that some of the structures observed in experiments are metastable in nature. Critical point of phase separation for this model shifts to lower $u_b$ compared to isotropic square well fluids [27]. It will be interesting to study the kinetics as well as the structural properties by varying patch sizes, shape of particles.

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ORCID iDs

Isha Malhotra https://orcid.org/0000-0002-9442-6621

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