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Wang, Haiqiang; Forsman, Jan; Woodward, Clifford E.

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PO Box 117
221 00 Lund
+46 46-222 00 00

Density Functional Theory of Equilibrium Random Copolymers: Application to Surface Adsorption of Aggregating Peptides

Haiqiang Wang

School of Physical,

Environmental and Mathematical Sciences

University of New South Wales,

Canberra at the Australian Defence Force Academy

Canberra ACT 2600, Australia

Jan Forsman*

Theoretical Chemistry,

Chemical Centre, Lund University

P.O.Box 124, S-221 00 Lund, Sweden

Clifford E. Woodward*†

School of Physical,

Environmental and Mathematical Sciences

University of New South Wales,

Canberra at the Australian Defence Force Academy

Canberra ACT 2600, Australia

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Abstract

We generalize a recently developed polymer density functional theory (PDFT) for polydisperse polymer fluids to the case of equilibrium random copolymers. We show that the generalization of the PDFT to these systems allows us to obtain a remarkable simplification compared to the monodispersed polymers. The theory is used to treat a model for protein aggregation into linear filaments in the presence of surfaces. Here we show that, for attractive surfaces, there is evidence of significant enhancement of protein aggregation. This behaviour is a consequence of a surface phase transition, which has been shown to occur with ideal equilibrium polymers in the presence of sufficiently attractive surfaces. For excluding monomers, this transition is suppressed, though an echo of the underlying ideal transition is present in the sudden change in the excess adsorption.

*Electronic address: jan.forsman@teokem.lu.se

†Electronic address: c.woodward@adfa.edu.au

I. INTRODUCTION

Polymers are profoundly affected by the presence of surfaces, a property which is relevant to many industrial and biological phenomena, such as colloidal stability and protein crystallization [1, 2]. Polymer density functional theory, PDFT, has proven to be a powerful theoretical tool for the treatment of polymer fluids and solutions at interfaces, furnishing accurate predictions for both structure and thermodynamic properties [3–7].

In the past, PDFT has focused on monodispersed chains [3, 8–10]. This is despite the fact that laboratory samples of polymers rarely possess chains of a fixed molecular weight, but generally display a degree of polydispersity. While polydispersity introduces additional complexity in the theoretical treatment of polymer fluids, it can be viewed as a potentially useful *control parameter* in such systems, allowing the tuning of physical properties, such as polymer adsorption and interfacial forces. This has made it desirable to find accurate theoretical treatments for polydispersed polymer fluids. For example, Tuinier and Pethukhov have used a product function approximation to study polydispersity effects on depletion by ideal chains [11]. The case of equilibrium polymers has been studied by van der Gucht and co-workers [12–14], using Scheutjens-Fleer theory [15], as well as the Edwards-deGennes self-consistent-field (SCF) theory [16–18]. More recently, Besseling and Korobko [19] have used SCF theory to study the adsorption of hard sphere equilibrium polymers between two surfaces. In other work, the effect of polydispersity has been treated by numerically averaging monodispersed solutions over the molecular weight distribution function using quadrature methods [20–22] and Yang *et al* [23] have studied the effect of polydispersity on the depletion interaction between non-adsorbing surfaces using such an approach.

Recently, we showed how the PDFT could be easily generalized to include polydispersity, when the molecular weight distribution is of the Schulz-Flory (SF) form [24]. Surprisingly, it was found that the algebraic structure of the PDFT was simpler than that for the monodispersed fluid and this manifested itself in a numerically more efficient solution algorithm. The SF distribution encompasses the exponential molecular weight distribution (MWD) of equilibrium polymers. Indeed, at thermodynamic equilibrium, the cases of equilibrium polymers (with reversible bonding of monomers) and an exponential MWD with permanent bonds, are indistinguishable.

There are many types of macromolecular systems that can reversibly aggregate into

linear structures under appropriate conditions. A particularly interesting example is the aggregation of amyloid proteins into linear filaments. These structures are believed to be part of the process that form fibrils, which are implicated in diseases such as Alzheimer's and Parkinson's disease. There have been a number of theoretical attempts to model the kinetic and equilibrium behaviour of these protein aggregates. A simple model has been developed by van Gestel and de Leeuw [25], which describes the linear aggregation of a two-state protein model. Their work is a generalization of the Zimm-Bragg treatment of helix-coil transitions in finite length polymers, to account for reversible aggregation [26]. In the treatment by van Gestel and de Leeuw [25], the possibility of the linear filaments aggregating laterally into fully-formed fibrils was also considered.

We shall generalize the theory by van Gestel and de Leeuw to account for the presence of external potentials. The work we present here will not consider fibril formation, instead focusing on simpler linear aggregates. More specifically, we will consider the effects of surfaces on the process of filament formation. Recent experimental investigations have shown that the presence of surfaces, such as cell membranes, or even synthetic nanoparticles can significantly modify the aggregation of proteins compared to the bulk [27–31]. The PDFT, is particularly suited to the description of reversibly aggregating monomers next to surfaces. We consider an extension of the theory to include the possibility of different (countable) states of the constituent aggregating monomers. In the case of aggregating proteins, this generalization would allow us to account for different conformational states of the protein molecules. The resulting theory essentially corresponds to a density functional treatment of *equilibrium random copolymers*.

In the next section we will develop the formalism of our new theory., which is then applied to the problem of protein association in the presence of surfaces. Results are presented for a range of model parameters and the implications of our results for the formation of protein filaments near surfaces are discussed.

II. THEORY

A. Density Functional Theory for Polydispersed Polymers

Our derivation is based on earlier work for semi-flexible polydisperse polymers [3, 32, 33]. We begin with the exact canonical free energy density functional for an ideal, monodisperse polymer fluid of semi-flexible r -mers,

$$\begin{aligned} \beta F_r^{id} = & \int d\mathbf{R} N_r(\mathbf{R}) (\ln[N_r(\mathbf{R})] - 1) + \\ & \int d\mathbf{R} N_r(\mathbf{R}) \Phi^{(b)}(\mathbf{R}) + \int d\mathbf{r} n_r(\mathbf{r}) \psi^0(\mathbf{r}) + \\ & \int d\mathbf{R} N_r(\mathbf{R}) \sum_{i=1}^{r-2} E_B(\mathbf{r}_i, \mathbf{r}_{i+1}, \mathbf{r}_{i+2}) \end{aligned} \quad (1)$$

Here, β , is the inverse thermal energy. The r -point density, $N_r(\mathbf{R})$, is a function of the monomer positions, $\mathbf{R} = (\mathbf{r}_1, \dots, \mathbf{r}_r)$, where \mathbf{r}_i is the coordinate of monomer i . $\Phi^{(b)}(\mathbf{R})$ describes the intra-molecular connectivity modelled as nearest-neighbor, non-directional bonding, i.e.,

$$\Phi^{(b)}(\mathbf{R}) = \sum_{i=1}^{r-1} \phi^{(b)}(|\mathbf{r}_i - \mathbf{r}_{i+1}|) \quad (2)$$

The bending potential, E_B , imparts stiffness to the chain. Keeping this stiffness term complicates the algebra and in the exposition given in this work we shall assume it to be zero. We note, however, that the inclusion of stiffness is, in principle, straightforward. But here we choose to focus on *flexible* random copolymers. Finally, $\psi^0(\mathbf{r})$, is the external potential acting on the monomers. While Eq.(1) is appropriate for polymers under theta (Θ) conditions, when additional non-bonding interactions are present, the ideal functional must be supplemented with a suitable excess term, F^{ex} . This excess term accounts for short-ranged steric interactions as well as possible long-ranged attractions, depending upon the quality of the solvent.

Consider now the the case of polydisperse polymers with up to n_m different monomer types (labelled by $1, \dots, n_m$). We let the vector, $\mathbf{c} = (r, \mathbf{s})$, denote both the degree of polymerization r , and the primary sequence of monomer types, $\mathbf{s} = (s_1, s_2, \dots, s_r)$, where $s_k \in \{1, \dots, n_m\}$. A bulk fluid of such polymers can be characterized by the average density of all polymer species, ϕ_p , and the fractional distribution of polymer types, $F(\mathbf{c})$. This distribution gives the fraction of species with primary structure given by \mathbf{c} and is normalized

according to

$$\sum_{\mathbf{c}} F(\mathbf{c}) = 1 \quad (3)$$

The chemical potential of the various polymer species is given by,

$$\beta\mu_{\mathbf{c}} = \ln[\phi_p F(\mathbf{c})] + \beta\Delta\mu_{\mathbf{c}}(bulk) \quad (4)$$

where $\Delta\mu_{\mathbf{c}}(bulk)$ is the excess chemical potential, which is zero for Θ conditions. In addition to bound species, there are *free* monomers (of type i), with density $n_i^f(\mathbf{r})$ and chemical potential μ_i^f .

When the fluid is subject to a spatially varying external potential, non-uniform density profiles result. These densities minimize the Gibb's free energy functional,

$$\Omega = F^{id} + F^{ex}[\{n_i^\alpha(\mathbf{r})\}] - \sum_{\mathbf{c}} \mu_{\mathbf{c}} \int d\mathbf{R} N_{\mathbf{c}}(\mathbf{R}) - \sum_i \mu_i^f \int d\mathbf{r} n_i^f(\mathbf{r}) \quad (5)$$

The first term of the RHS of Eq.(5) is the ideal contribution, and is the generalization of Eq.(1) to a mixture

$$\begin{aligned} \beta F^{id} = & \sum_{\mathbf{c}} \int d\mathbf{R} N_{\mathbf{c}}(\mathbf{R}) (\ln[N_{\mathbf{c}}(\mathbf{R})] - 1) + \sum_i \int d\mathbf{r} n_i^f(\mathbf{r}) (\ln[n_i^f(\mathbf{r})] - 1) + \\ & \sum_{\mathbf{c}} \int d\mathbf{R} N_{\mathbf{c}}(\mathbf{R}) \Phi_{\mathbf{c}}^{(b)}(\mathbf{R}) + \sum_i \int d\mathbf{r} n_i^{tot}(\mathbf{r}) \psi_i^0(\mathbf{r}) \end{aligned} \quad (6)$$

In this expression we have specifically separated the free monomer species and also accounted for the possibility that the monomer types will have different interactions with the external potential.

We let, $n_i^\alpha(\mathbf{r})$, denote the density of type i monomers with *connectivity* denoted by α . The different types of monomer connectivities are:

- monomers with two bonded neighbours
- monomers with a single bonded neighbour
- monomers with no bonds (free).

The total monomer density is $n_i^{tot}(\mathbf{r}) = \sum_{\alpha} n_i^\alpha(\mathbf{r})$. As with most DFT approaches, we shall assume that the excess free energy, $F^{ex}[\{n_i^\alpha(\mathbf{r})\}]$, is a functional only of these monomer densities. If we assume that only steric interactions act between monomers, the system is

denoted as *athermal*, which corresponds to a particular type of good solvent. In principle, this excess free energy term should then be sensitive to the monomer connectivity, due to cooperativity in excluded volume overlaps. In short, a free monomer excludes more volume to other particles than a bound monomer, as bound neighbours will have overlapping excluded volume. Hence, bound monomers at chain ends exclude more volume than those in the interior part of the chain. For simplicity, in the current theoretical development, we shall only differentiate *free* and *bound* monomers, where the latter is the sum of densities of those monomers with either one or two bonded neighbours. Later, when we apply the theory to adsorbing peptides, we shall remove this distinction altogether.

B. Self-Assembling Random Copolymers

1. Bulk System

We now consider polymer molecules, which result from the reversible self-assembly of monomers into linear chains. Hence, the total chemical potential of all monomer species is set by the concentration of free monomers in the bulk, denoted by $\{n_i^f(bulk); i = 1, n_m\}$. For the case of only one monomer type, the bulk distribution, $F(\mathbf{c})$, will depend only upon the degree of polymerization, r . For ideal polymers it will be given by an exponential distribution,

$$F(r) = Ke^{-\kappa r} \quad (7)$$

with K a normalization factor and $\kappa^{-1} = \langle r \rangle_b$ is the average polymer length in the bulk. Even for non-ideal polymers, the exponential distribution is a reasonably good approximation for long enough polymers due to the fact that (to a good approximation) the excess chemical potential scales as the degree of polymerization, r .

When different monomer types are present, the bulk distribution is determined by considering all possible monomer combinations. This problem can be mapped onto a 1-dimensional Ising chain with an applied magnetic field, an approach used by van Gestel *et al* to study helical transitions in equilibrium polymers [34] and more recently for associating proteins

[25]. The distribution of aggregate lengths, $f(r) = \sum_{\mathbf{s}} F(\mathbf{c})$, will be given by

$$f(r) = Q(r) / \sum_r Q(r) \quad (8)$$

where the Grand partition function for the r -mer ($r > 1$) is given by, the expression,

$$Q(r) = \mathbf{u} \cdot \mathbf{T}^{r-1} \cdot \mathbf{f}^\dagger \quad (9)$$

The transfer matrix \mathbf{T} is given by the expression

$$\mathbf{T} = \begin{bmatrix} f_1 t_{11} & f_1 t_{12} & \cdots & f_1 t_{1n_m} \\ f_2 t_{21} & f_2 t_{22} & \cdots & f_2 t_{2n_m} \\ \vdots & \vdots & \ddots & \vdots \\ f_{n_m} t_{n_m 1} & f_{n_m} t_{n_m 2} & \cdots & f_{n_m} t_{n_m n_m} \end{bmatrix} \quad (10)$$

where f_i is the bulk fugacity of the *free* monomer of type i

$$f_i = n_i^f(\text{bulk}) e^{\beta \Delta \mu_i^f(\text{bulk})} \quad (11)$$

where $\Delta \mu_i^f(\text{bulk})$ is the excess chemical potential (beyond the ideal fluid) of the free monomer of type i in the bulk fluid. The quantity $t_{ij} = e^{-\beta g_{ij}}$, where g_{ij} , is the free energy of the bonded monomers of type i and j . The terminal vectors are given by

$$\mathbf{f}^\dagger = \begin{pmatrix} f_1 \\ \vdots \\ f_{n_m} \end{pmatrix} \quad (12)$$

and

$$\mathbf{u} = (1, 1 \dots 1) \quad (13)$$

Variation of these terminal vectors allows the investigation of end-effects on the molecular weight distribution. For example, a model used to study associating proteins found that the lengths of filaments formed can be significantly affected by the configurational state of the terminal proteins [25]. The Mass Action Law gives the following expression for the bulk copolymer densities, $N_{\mathbf{c}}(\text{bulk})$, with primary structure \mathbf{c} ,

$$N_{\mathbf{c}}(\text{bulk}) = f_{s_r} \prod_{i=1}^{r-1} T_{s_i, s_{i+1}} \quad (14)$$

We note that $N_{\mathbf{c}} = \phi_p F(\mathbf{c})$ and T_{ij} are the elements of the transfer matrix, Eq.(10).

2. Non-uniform System

Suppose the polymer fluid is subject to an external potential, $\psi_k^0(\mathbf{r})$ which acts on the different monomer types $k = 1..n_m$. We shall assume that the external potential is zero in the bulk fluid. The equilibrium polymer density becomes spatially dependent and is obtained by minimizing the free energy functional, Ω , Eq.(5). This gives the following self-consistent expression for the density of aggregates of dimers and greater ($r > 1$),

$$N_{\mathbf{c}}(\mathbf{R}) = N_{\mathbf{c}}(bulk)e^{\beta\Delta\mu_{\mathbf{c}}(bulk)} \prod_{i=1}^r e^{-\beta\psi_{s_i}^b(\mathbf{r}_i)} \prod_{i=1}^{r-1} \Theta_{s_i s_{i+1}}(|\mathbf{r}_i - \mathbf{r}_{i+1}|) \quad (15)$$

Here we have defined,

$$\psi_i^b(\mathbf{r}) = \frac{\delta F^{ex}}{\delta n_i^b(\mathbf{r})} + \psi_i^0(\mathbf{r}) \quad (16)$$

where $n_i^b(\mathbf{r})$ is density of *bound* monomers and F^{ex} is the excess free energy of the non-uniform fluid, from Eq.(5). Also,

$$\Theta_{kl}(|\mathbf{r} - \mathbf{r}'|) = e^{-\phi_{kl}^{(b)}(|\mathbf{r} - \mathbf{r}'|)} \quad (17)$$

The excess (beyond the ideal) bulk chemical potential of the chains with primary structure, \mathbf{c} , is given by

$$\beta\Delta\mu_{\mathbf{c}}(bulk) = \sum_{i=1}^r \beta\psi_{s_i}^b(bulk) - \sum_{i=1}^{r-1} \ln \left[\int d\mathbf{r}' \Theta_{s_i s_{i+1}}(|\mathbf{r} - \mathbf{r}'|) \right] \quad (18)$$

The first term on the RHS of Eq.(18) describes the effect of the medium on the chemical potential of the bound monomers It is equal to the RHS of Eq.(16) in the bulk, i.e.,

$$\beta\psi_i^b(bulk) = \psi_i^b(\mathbf{r}), \text{ for all } \mathbf{r} \in \text{bulk} \quad (19)$$

The second term on the RHS of Eq.(18) is the free energy of the *ideal* chain with one end pinned. Substituting this expression for the chemical potential into Eq.(15) gives,

$$N_{\mathbf{c}}(\mathbf{R}) = N_{\mathbf{c}}(bulk) \prod_{i=1}^r e^{-\beta\Delta\psi_{s_i}^b(\mathbf{r}_i)} \prod_{i=1}^{r-1} \frac{\Theta_{s_i s_{i+1}}(|\mathbf{r} - \mathbf{r}'|)}{\int d\mathbf{r}' \Theta_{s_i s_{i+1}}(|\mathbf{r} - \mathbf{r}'|)} \quad (20)$$

where $\Delta\psi_i^b(\mathbf{r}) = \psi_i^b(\mathbf{r}) - \beta\psi_{s_i}^b(bulk)$. Finally, using Eq.(14), we obtain

$$N_{\mathbf{c}}(\mathbf{R}) = \prod_{i=1}^r f_{s_i} e^{-\beta\Delta\psi_{s_i}^b(\mathbf{r}_i)} \prod_{i=1}^{r-1} T_{s_i s_{i+1}}(|\mathbf{r}_i - \mathbf{r}_{i+1}|) \quad (21)$$

where

$$T_{lk}(|\mathbf{r}' - \mathbf{r}|) = t_{lk} \frac{\Theta_{lk}(|\mathbf{r}' - \mathbf{r}|)}{\int d\mathbf{r}' \Theta_{lk}(|\mathbf{r}' - \mathbf{r}|)} \quad (22)$$

which is the generalization of Eq.(14) to non-uniform fluids. The above equations represent a closed system, which must be solved self-consistently in order to generate the thermodynamic properties of the system.

In order to calculate the required monomer densities, it is useful to introduce the following modified distribution functions for chain segments of length n (≥ 2)

$$c_{s_n}(n; \mathbf{r}_n) = \int d\mathbf{r}_1 \dots \int d\mathbf{r}_{n-1} \sum_{s_1} \dots \sum_{s_{n-1}} \prod_{i=1}^{n-1} f_{s_i} e^{-\beta \Delta \psi_{s_i}^b(\mathbf{r}_i)} T_{s_i s_{i+1}}(|\mathbf{r}_i - \mathbf{r}_{i+1}|) \sqrt{f_{s_n}^b} e^{-\beta \Delta \psi_{s_n}^b(\mathbf{r})/2} \quad (23)$$

and, for $n = 1$,

$$c_k(1; \mathbf{r}) = \sqrt{f_k} e^{-\beta \Delta \psi_k^b(\mathbf{r})/2}. \quad (24)$$

The average total density of (bound) monomers of type k is given by,

$$n_k^b(\mathbf{r}) = \sum_{n=1}^{\infty} \sum_{m=1}^{\infty} c_k(n; \mathbf{r}) c_k(m; \mathbf{r}) - c_k(1; \mathbf{r})^2 \quad (25)$$

where the second term on the RHS of Eq.(25) corrects for the spurious non-bonded term ($n, m = 1$). This expression can be rewritten more succinctly as,

$$n_k^{(b)}(\mathbf{r}) = \bar{c}_k(\mathbf{r}) \bar{c}_k(\mathbf{r}) - c_k(1; \mathbf{r})^2 \quad (26)$$

where

$$\bar{c}_k(\mathbf{r}) = \sum_{n=1}^{\infty} c_k(n; \mathbf{r}) \quad (27)$$

The density of free monomers is given by

$$n_k^f(\mathbf{r}) = f_k e^{-\beta \Delta \psi_k^f(\mathbf{r})} \quad (28)$$

where,

$$\Delta \psi_k^f(\mathbf{r}) = \frac{\delta F^{ex}}{\delta n_k^f(\mathbf{r})} + \psi_k^0(\mathbf{r}) \quad (29)$$

Given the definitions Eq.s (23) and (27), one can obtain the following simple recursion formula,

$$\bar{c}_k(\mathbf{r}) = \sum_{l=1}^{n_m} \int d\mathbf{r}' \bar{c}_l(\mathbf{r}') M_{lk}(\mathbf{r}, \mathbf{r}') + \sqrt{f_k} e^{-\beta \Delta \psi_k^b(\mathbf{r})/2} \quad (30)$$

where

$$M_{lk}(\mathbf{r}', \mathbf{r}) = \sqrt{f_l} e^{-\beta \Delta \psi_l^b(\mathbf{r}')/2} t_{lk} T_{lk}(|\mathbf{r}' - \mathbf{r}|) \sqrt{f_k} e^{-\beta \Delta \psi_k^b(\mathbf{r})/2} \quad (31)$$

which can be written in matrix form as,

$$\bar{\mathbf{c}} = \bar{\mathbf{c}} \mathbf{M} + \mathbf{v} \quad (32)$$

where \mathbf{M} is the symmetric matrix with elements, $M_{lk}(\mathbf{r}', \mathbf{r})$ with the vector $\bar{\mathbf{c}} = (\bar{c}_1(\mathbf{r}) \dots \bar{c}_{n_m}(\mathbf{r}))$ and $\mathbf{v} = (\sqrt{f_1} e^{-\beta \Delta \psi_1^b(\mathbf{r})/2} \dots \sqrt{f_{n_m}^b} e^{-\beta \Delta \psi_{n_m}^b(\mathbf{r})/2})$. The generalized matrix vector product is given by

$$\sum_{l=1}^{n_m} \int d\mathbf{r}' \bar{c}_l(\mathbf{r}') M_{lk}(\mathbf{r}', \mathbf{r}) \quad (33)$$

C. End-Effects

The expressions above make the assumption that all monomers in the aggregate chains are in equilibrium with the bulk. It may be desirable to consider situations where the distribution of terminal monomer types in the bulk are fixed *a priori*. We use A, B to label the two ends of a linear aggregate which is modified from its equilibrium distribution via the weights, $\mathbf{P}^{(A)} = (p_1^{(A)}, \dots, p_{n_m}^{(A)})$. These weights affect the end vector as follows, $\mathbf{v}^{(A)} = (p_1^{(A)} \sqrt{f_1} e^{-\beta \Delta \psi_1^b(\mathbf{r})/2} \dots p_{n_m}^{(A)} \sqrt{f_{n_m}^b} e^{-\beta \Delta \psi_{n_m}^b(\mathbf{r})/2})$ and the recursion formula, Eq(30), becomes,

$$\bar{\mathbf{c}}^{(A)} = \bar{\mathbf{c}}^{(A)} \mathbf{M} + \mathbf{v}^{(A)} \quad (34)$$

These new end-point distributions can be used to generate the (bound) monomer densities in an equilibrium random copolymer, with different with different types of ends, A and B . These are given by,

$$n_k^b(\mathbf{r}) = \bar{c}_k^{(A)}(\mathbf{r}) \bar{c}_k^{(B)}(\mathbf{r}) - p_k^{(A)} f_k e^{-\beta \Delta \psi_k^b(\mathbf{r})} p_k^{(B)} \quad (35)$$

III. PROTEIN AGGREGATION ON SURFACES

The theory presented above is quite general and can be applied to a wide range of molecular models over a diverse range of length-scales. Here, we will consider the problem of protein aggregation on surfaces. In this case, the monomer size is of the order of nanometers. We shall generalize a protein aggregation model for the $A\beta$ peptide (which is linked to Alzheimer's Disease) proposed by van Gestel and de Lueew. This model describes the

formation of protein filaments and their association into fibrils in a bulk solution. Using the PDFT above we will generalize this model so as to describe the association of protein filaments in the presence of surfaces.

In the theory of van Gestel and de Lueew, a filament consists of a random linear aggregate of two “monomer” types. One is the $A\beta$ peptide in a β -strand form, which is able to participate in so-called *cross- β* sheet hydrogen bonding with neighboring peptides having a similar conformation. The other monomer type is a disordered peptide structure, which associates more weakly, but is the preferred conformation at the terminals of the filaments. We shall label these as the β -strand (β) and *disordered* (d) forms of the $A\beta$ peptide. Fibrils consist of several filaments associated via steric zipper interactions [35, 36]. While fibril formation is often associated with amyloid diseases, it is now widely conjectured that smaller oligomeric aggregates are more likely responsible for cell death, presumably through adsorption onto cell membranes, leading to their eventual disruption [37–40]. It is likely that these oligomers are not mature fibrils, but have a structure better represented by the simpler filaments. Thus, in this study, we shall only consider the interaction between linear peptide filaments and surfaces.

A. Filament distribution in the bulk

From Eq.(15), we see that the non-uniform theory requires the distribution of aggregates in the bulk fluid as input. In the theory of van Gestel and de Lueew, the water solvent is treated implicitly and it is assumed that the long-ranged (dispersion) interaction between the peptides is relatively weak. The primary structure of a filament is determined by the nearest neighbor bonding free energy and the availability of monomers, determined by their bulk fugacity, f_k . Monomer types at the terminals of the filaments were assumed to be in the d conformation [25]. This choice was based on the idea that β -strands are stabilized by a sufficient number of adjacent peptides especially when they are also in a β conformation.

As already noted above, the thermodynamic properties of the bulk can be obtained by mapping onto a 1-dimensional Ising chain in a magnetic field, which is then solved using standard transfer matrix methods. The details are provided in the original reference [25], so we will only report the results of relevance to the current study. For example, the number

density of oligomers of length, $r (\geq 2)$, is given by,

$$\rho(r) = z^r q(r) \quad (36)$$

where z is the fugacity of the free monomers of the disordered peptide and $q(r)$ is the partition function of an oligomer containing r monomers (of either type). An explicit expression for $q(r)$ can be obtained in terms of the eigenvalues of the 2×2 transfer matrix,

$$q(r) = (x\lambda_1^{r-2} + y\lambda_2^{r-2})k^{r-1} \quad (37)$$

with $x = (\lambda_1 - s)/(\lambda_1 - \lambda_2)$ and $y = (s - \lambda_2)/(\lambda_1 - \lambda_2)$. The eigenvalues are given by

$$\lambda_{1,2} = \frac{1}{2} + \frac{s}{2} \pm \frac{((1-s)^2 + 4s\sigma)^{1/2}}{2} \quad (38)$$

These parameters reflect the various interaction energies between the bound monomers with $k = \exp(-M)$; $s = \exp(-P)$, and $\sigma^{1/2} = \exp(-R)$. Here M is the binding free energy between d conformers. P is the additional free energy upon binding two peptides in β conformations. Finally, R represents the cost of creating an interface between a bound peptide pair in β and d conformations respectively. We can define the normalized distribution for r -mers, $r(\geq 2)$,

$$f(r) = \frac{z^r q(r)}{\sum_{r=1}^{\infty} z^r q(r)} \quad (39)$$

Here, we make the implicit substitution, $q(1) = 1$, in the denominator sum. Upon substitution of Eq.(37) we obtain,

$$f(r) = K_1(\lambda_1 k z)^r + K_2(\lambda_2 k z)^r \quad (40)$$

where

$$K_1 = \frac{\frac{x}{\lambda_1^2}}{\frac{x}{\lambda_1^2} \frac{\lambda_1 k z}{1 - \lambda_1 k z} + \frac{y}{\lambda_2^2} \frac{\lambda_2 k z}{1 - \lambda_2 k z}} \quad (41)$$

and

$$K_2 = \frac{\frac{y}{\lambda_2^2}}{\frac{x}{\lambda_1^2} \frac{\lambda_1 k z}{1 - \lambda_1 k z} + \frac{y}{\lambda_2^2} \frac{\lambda_2 k z}{1 - \lambda_2 k z}} \quad (42)$$

In this study, use the following parameter values $s = 70$ and $\sigma = 0.1$, which are the same as those used in the work by van Gestel and de Leeuw [25]. These parameters give the free energies associated with β - β bonding and β - d interfaces in excess of an underlying chain of d conformers. The free energy of this underlying chain is determined by the value of the

product zk , which is the excess fugacity associated with removing a peptide from the bulk and creating a (shared) d - d bond. Choosing the average filament length in the bulk $\langle r \rangle_b$ allows us to obtain the product zk from the following expression (obtained as an appropriate average over the distribution $f(r)$) [25],

$$\langle r \rangle_b = \frac{zk + \sum_{r=2} z^r k q(r) r}{zk + \sum_{r=2} z^r k q(r)} \quad (43)$$

The bulk protein density, $n^{tot}(bulk)$, then gives the individual z and k values, using the following expression for the number density of r -mers [25],

$$\Phi_p^{tot} = \frac{n^{tot}(bulk)}{\langle r \rangle_b} = z + z \left(\frac{zkx}{1 - \lambda_1 zk} + \frac{zky}{1 - \lambda_2 zk} \right) \quad (44)$$

where Φ_p^{tot} , is the overall oligomer density of the bulk.

B. Simplified Model for Protein Adsorption

The oligomer distribution Eq.(40) provides a starting point for a simplified model for protein surface aggregation. We shall assume a flat surface which adsorbs both β and d conformers of the peptide equally well. This treatment ignores scenarios where conformational changes in the peptide affect their surface interactions in a significant way, e.g., functionalized surfaces may interact with specific peptide sites, which become accessible upon conformational change. Instead, we consider situations where the the conformational changes associated with the $d \rightarrow \beta$ transition has greater implications on the peptide-peptide interaction, rather than on peptide-surface interactions. This is likely to be the case for the $A\beta$ peptide, which forms strong cross- β sheets. It is worth noting, however, that the generalization of the theory to account for conformation dependent surface interactions is relatively straightforward. We shall also assume that conformational changes will not cause significant changes in the size (excluded volume) of the peptides. With these assumptions, the local excess chemical potential for bound monomers, Eq.(16), becomes independent of monomer type. Thus it is useful to define,

$$\psi^b(\mathbf{r}) = \frac{\delta F^{ex}}{\delta n^b(\mathbf{r})} + \psi^0(\mathbf{r}) \quad (45)$$

and

$$\Delta\psi^b(\mathbf{r}) = \psi^b(\mathbf{r}) - \psi^b(bulk) \quad (46)$$

where $n^b(\mathbf{r})$ is the total bound monomer density, and $\psi^0(\mathbf{r})$ is the generic surface-protein interaction. Additionally, the bonding factor has the following simpler form,

$$T_{lk}(|\mathbf{r}' - \mathbf{r}|) = t_{lk}t(|\mathbf{r}' - \mathbf{r}|) \quad (47)$$

with $t(|\mathbf{r}' - \mathbf{r}|)$ describing monomer-monomer bonding. In this application we shall assume the bonding has the simple form,

$$t(|\mathbf{r} - \mathbf{r}'|) = \frac{\delta(|\mathbf{r} - \mathbf{r}'| - \sigma)}{4\pi\sigma^2} \quad (48)$$

with $\delta(r)$ the Dirac delta function and σ is the nearest-neighbour bonding length-scale of the aggregating peptides. Using Eq.(25), we sum over the monomer type k to get the total bound monomer density,

$$n^b(\mathbf{r}) = \sum_{k=\beta,d} \sum_{n=1}^{\infty} \sum_{m=1}^{\infty} c_k(n; \mathbf{r})c_k(m; \mathbf{r}) - \sum_{k=\beta,d} c_k(1; \mathbf{r})^2 \quad (49)$$

From the definition of $c_k(n; \mathbf{r})$ in Eq.(23), we can rewrite Eq.(49) as,

$$n^b(\mathbf{r}) = \sum_{n=1}^{\infty} \sum_{m=1}^{\infty} \Phi_p f(n+m-1) c(n; \mathbf{r}) c(m; \mathbf{r}) - \Phi_p f(1) c(1; \mathbf{r})^2 \quad (50)$$

where we define the simpler end-point distribution,

$$c(n; \mathbf{r}_n) = \int d\mathbf{r}_1 \dots \int d\mathbf{r}_{n-1} \prod_{i=1}^{n-1} e^{-\beta\Delta\psi^b(\mathbf{r}_i)} t(|\mathbf{r}_i - \mathbf{r}_{i+1}|) e^{-\beta\Delta\psi^b(\mathbf{r}_n)/2} \quad (51)$$

which satisfies the following recursion formula

$$c(n+1, \mathbf{r}) = \int d\mathbf{r}' e^{-\beta\Delta\psi^b(\mathbf{r})/2} t(|\mathbf{r} - \mathbf{r}'|) e^{-\beta\Delta\psi^b(\mathbf{r}')/2} c(n, \mathbf{r}') \quad (52)$$

with initial condition,

$$c(1, \mathbf{r}) = \exp(-\beta\Delta\psi^b(\mathbf{r})/2) \quad (53)$$

Using Eq.(40), we obtain

$$\begin{aligned} n^b(\mathbf{r}) = & \Phi_p \sum_{n=1}^{\infty} \sum_{m=1}^{\infty} \frac{K_1}{\lambda_1 k z} (\lambda_1 k z)^n c(n, \mathbf{r}) (\lambda_1 k z)^m c(m, \mathbf{r}) \\ & + \Phi_p \sum_{n=1}^{\infty} \sum_{m=1}^{\infty} \frac{K_2}{\lambda_2 k z} (\lambda_2 k z)^n c(n, \mathbf{r}) (\lambda_2 k z)^m c(m, \mathbf{r}) - \Phi_p f(1) c(1; \mathbf{r})^2 \end{aligned} \quad (54)$$

Defining,

$$\bar{c}_i(\mathbf{r}) = \sum_{n=1}^{\infty} (\lambda_i k z)^n c(n, \mathbf{r}) \quad (55)$$

where $i = 1, 2$, we obtain

$$n^b(\mathbf{r})\Phi_p^{-1} = \frac{K_1}{\lambda_1 k z} \bar{c}_1(\mathbf{r})\bar{c}_1(\mathbf{r}) + \frac{K_2}{\lambda_2 k z} \bar{c}_2(\mathbf{r})\bar{c}_2(\mathbf{r}) - f(1)c(1; \mathbf{r})^2 \quad (56)$$

From Eq.(52) and the definition Eq.(55), the following recursion formula applies,

$$\bar{c}_i(\mathbf{r}) - \lambda_i k z c(1, \mathbf{r}) = \lambda_i k z \int d\mathbf{r}' e^{-\beta \Delta \psi^b(\mathbf{r})/2} t(|\mathbf{r} - \mathbf{r}'|) e^{-\beta \Delta \psi^b(\mathbf{r}')/2} \bar{c}_i(\mathbf{r}') \quad (57)$$

Eq.s (45), (56) and (57) provide a self-consistent set of equations which can be used to solve for the density and free energy of protein filaments adsorbed onto surfaces.

C. The excess free energy

Different versions of PDFT arise from the choice of excess functional F^{ex} in Eq.(5) [3–7, 41–47]. We used three different models for the excess free energy. In the first model we assume that water is a Θ solvent for the peptides, so that the excess free energy is zero. In the other two models, steric interactions are assumed to act between the peptides, which we model as effective hard spheres with a radius independent of the peptide conformation (d or β). For hard sphere interactions a good accuracy has been found with the so-called Generalised Flory-Dimer (GFD) functional for the excess free energy, F^{ex} [4, 43] Numerous tests have verified that this also pertains to structural properties in heterogeneous systems, containing monodisperse polymers [46, 47]. Corresponding tests of polydisperse solutions have not been performed, as these would require expensive and cumbersome simulations. This functional will be used in the present problem.

It is convenient to express the excess free energy in the following form,

$$\beta F^{ex} = \int d\mathbf{r} n_{tot}(\mathbf{r}) a^{ex}(\eta) d\mathbf{r} \quad (58)$$

where $n_{tot}(\mathbf{r})$ is the total peptide density. Here $a^{ex}(\eta)$ is the local free energy per particle and η is a measure of the volume fraction, which is a functional of the total peptide density. In the GFD approximation $a^{ex}(\eta)$ is given by the general expression [4, 43],

$$a^{ex}(\eta) = -\frac{c_i + 1}{2} \ln(1 - \eta) - \frac{(2c_i - 2a_i - 4)\eta + (3 - b_i + a_i - 3c_i)\eta^2}{(1 - \eta)^2} \quad (59)$$

where

$$a_1 = 1, a_2 = 2.45696 \quad (60)$$

$$b_1 = 1, b_2 = 4.10386 \quad (61)$$

$$c_1 = 0, c_2 = -3.75503 \quad (62)$$

We denote the two versions of the steric model as *local* and *non-local*. The local model is similar in spirit to the incompressibility assumption, used in the Flory-Huggins theory. If one assumes incompressibility at every point in the solution, we obtain a simplified excluded volume term between monomers. If we use the GFD functional to treat this, the quantity η in Eq.(58) is given by a local volume fraction, i.e., $\eta = (\pi\sigma^3 n_{tot}(\mathbf{r}))/6$, where the bond-length, σ , between peptides in the filament is also assumed to be equal to the peptide diameter. Our other model employs a non-local version of this functional with a *weighted* density that accounts for the possibility of short-ranged structuring. The functional has the form, $\eta = [(\pi\sigma^3 \bar{n}_{tot}(\mathbf{r}))/6]$ where,

$$\bar{n}_{tot}(\mathbf{r}) = \frac{3}{4\pi\sigma^3} \int_{|\mathbf{r}-\mathbf{r}'|<\sigma} d\mathbf{r}' n_{tot}(\mathbf{r}') \quad (63)$$

IV. THE SURFACE POTENTIAL

The interaction between the surface and peptide conformers is modelled as a truncated and shifted Lennard-Jones potential, integrated over the half-space of the surface, i.e.,

$$\psi^0(z) = \begin{cases} \omega_{LJ}(z) - \omega_{LJ}(z_c), & \text{for } z < z_c \\ 0 & \text{otherwise} \end{cases} \quad (64)$$

where

$$\beta\omega_{LJ}(z) = 10\pi \left[\frac{2}{45} \left(\frac{\sigma}{z}\right)^9 - \frac{a_w}{3} \left(\frac{\sigma}{z}\right)^3 \right] \quad (65)$$

The coordinate z is the perpendicular distance from the surface and we have set $z_c = 4\sigma$. The strength of the surface attraction is determined by the parameter, a_w . Due to the form of this external potential, this system has a planar geometry and the densities which minimise the free energy will only depend on z

V. RESULTS AND DISCUSSION

A. Ideal peptide model

Fig. 1 shows the density of peptide bound in filaments as a function of distance from the surface for various values of the attractive part of the surface potential, as parameterized by the quantity a_w . The average filament length in the bulk was set at $\langle r \rangle_b = 2$. In the ideal model, the steric effect of the peptides is not accounted for. At low surface attraction, it is clear that there is a depletion of monomers close to the surface due to the decrease in configurational entropy. However, as the attraction on the surface increases, the peptide concentration starts to build. Indeed, for a_w slightly greater than 0.07, we find that the monomer density on the surface goes to infinity. When the surface attraction reaches a certain critical value, the density of the adsorbed peptide diverges, displaying the signature of a second order surface phase transition. This is the same *adsorption transition* observed by de Gennes for infinite polymers in a Θ solvent [17, 48]. However, it occurs here in a living polymer formed by aggregating peptide, displaying a dual exponential molecular weight distribution, Eq.(40). Hence this is essentially equivalent to a surface phase transition described by Sear [49] and which has also been reported by van der Gucht et al. [14], as well as Forsman and Woodward [50]. This transition is accompanied by an enormous growth in the average length of filaments close to the surface.

According to Sear [49], the surface phase transition occurs when the attraction is larger than $a_w \approx a_w(eq) + 1/\langle r \rangle_b^{1/2}$ where $a_w(eq)$ is the value which gives essentially zero excess adsorption ($\theta^{ex} = 0$) where the latter is defined as,

$$\theta^{ex} = \int_0^\infty (n^b(z) - n^b(bulk))dz \quad (66)$$

The value of a_w must be somewhat greater than $a_w(eq)$ for the surface transition to be observed. The greater the average bulk filament length, the closer to $a_w(eq)$ at which this transition will occur. In Fig. 2, we show the bound monomer density as a function of the distance from the surfaces for a number of average filament lengths. The strength of the surface adsorption is set at $a_w = 0.05$. It is clear from the profiles that $\theta^{ex} < 0$, i.e., $a_w < a_w(eq)$. Increasing the average length of the peptides in the bulk only serves to decrease the peptide density at the surfaces, due to the depletion effect. Indeed, one finds that the average length of peptide filaments close to the surfaces actually decreases below that of

the bulk value (not shown). In Fig. 3, we show the bound peptide density profiles for various average bulk filament lengths with $a_w = 0.065$ and $n^b(bulk)\sigma^3 = 0.001$. In this case $\theta^{ex} > 0$, for all the $\langle r \rangle_b$ investigated. The longer filaments have a higher density near the surface than the shorter ones, due to cooperative binding, and increasing the value of $\langle r \rangle_b$ eventually leads to the adsorption transition. We note here that for ideal polymers, the bulk density serves only as a multiplicative factor for the density profiles. This will not be the case for the peptide models which include steric interactions. The infinite surface

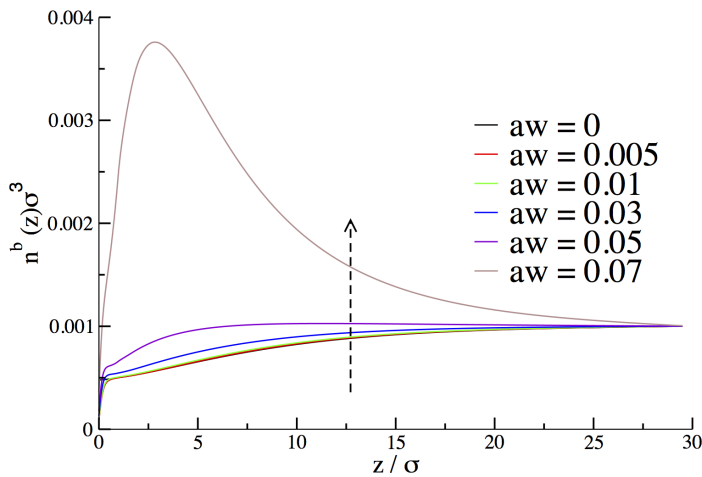


FIG. 1: Plot of $n^b(z)\sigma^3$ as a function of z/σ for ideal polymer for increasing surface attraction and $n^b(bulk)\sigma^3 = 10^{-3}$. The arrow indicates the direction of increasing a_w .

density that is implied by the adsorption transition is clearly unphysical. It occurs in the ideal model because of the lack of steric interactions. We expect the latter should act to suppress the transition. This can be verified by considering the models which include the effects of the hard core interactions, as will be done in the next section.

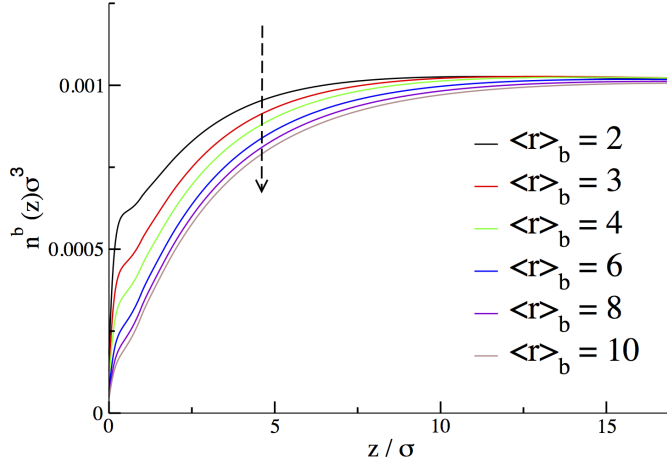


FIG. 2: Plot of $n^b(z)\sigma^3$ as a function of z/σ for different average lengths, $a_w = 0.05$ and $n^b(bulk)\sigma^3 = 10^{-3}$. The arrow indicates the direction of increasing $\langle r \rangle_b$.

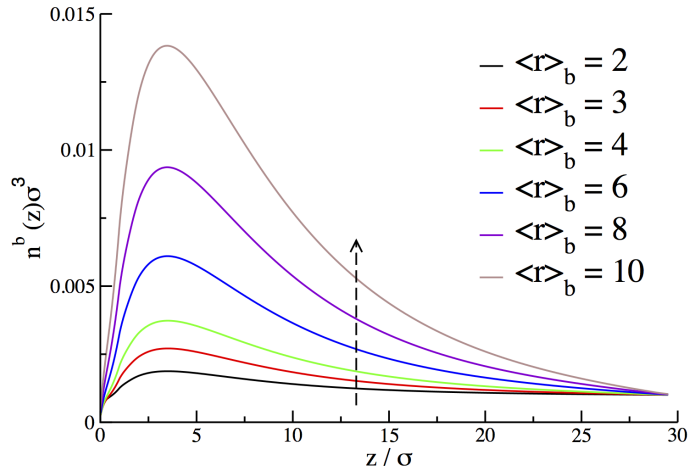


FIG. 3: Plot of $n^b(z)\sigma^3$ as a function of z/σ for different average lengths, $a_w = 0.065$ and $n^b(bulk)\sigma^3 = 10^{-3}$. The arrow indicates the direction of increasing $\langle r \rangle_b$.

B. Steric interactions - non-local theory

In this section peptides with steric interactions. The bound peptide density profiles for the case $\langle r \rangle_b = 2$ are plotted in Fig. 4 and 5 for different values of attraction parameter a_w . In Fig. 4, we see a similar behaviour to what is seen in the ideal model. However, when the surface attraction increases to quite large values (as shown in Fig. 5), the density remains finite due to peptide excluding one another at the surface. We note that the density adjacent to the surface can become large provided that the integral of the density within a certain distance of the order of σ from the surface is finite. In Fig. 5, there is clear evidence of peptide layering at the surface. This is due to hard sphere structuring, which is captured by the non-local functional, Eq.(63).

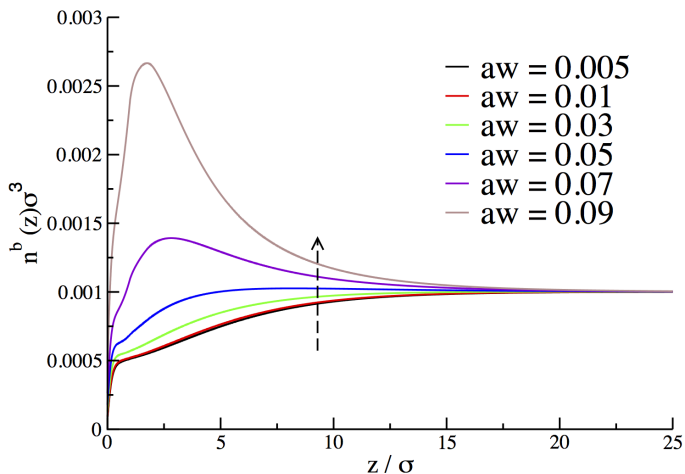


FIG. 4: Plot of $n^b(z)\sigma^3$ as a function of z/σ for polymer with hard sphere terms for increasing surface attraction and $n^b(bulk)\sigma^3 = 10^{-3}$. The arrow indicates the direction of increasing a_w .

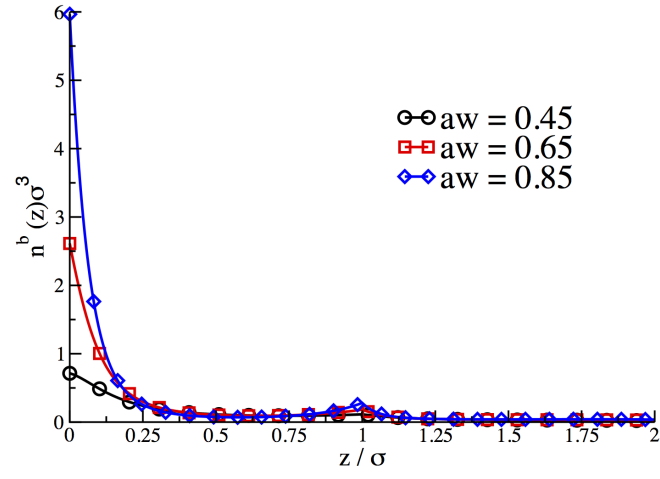


FIG. 5: Plot of $n^b(z)\sigma^3$ as a function of z/σ for polymer with hard sphere terms and larger attraction from the surface. The bound peptide density in the bulk $n^b(bulk)\sigma^3 = 10^{-3}$.

In Fig. 6 we plot the excess adsorption of bound peptide at the surface as function of the attraction strength, a_w , for various average filament lengths. Obviously, at very weak adsorption potential strength, the excess adsorption is low and clearly approaches negative values. We note that $a_w(eq)$ is rather independent of the average filament length, as can be ascertained by the quite sudden transition between positive and negative θ^{ex} . As the peptide are able to sterically exclude one another, the second-order adsorption transition does not occur in this system. However, we do expect to see a sudden increase in the excess adsorption at a particular value of a_w , which echoes the adsorption transition of the ideal system. This should appear as a point of inflection in the adsorption plot. Interestingly, we do not see strong evidence for this in Fig. 6, which would imply that steric effects suppresses it.

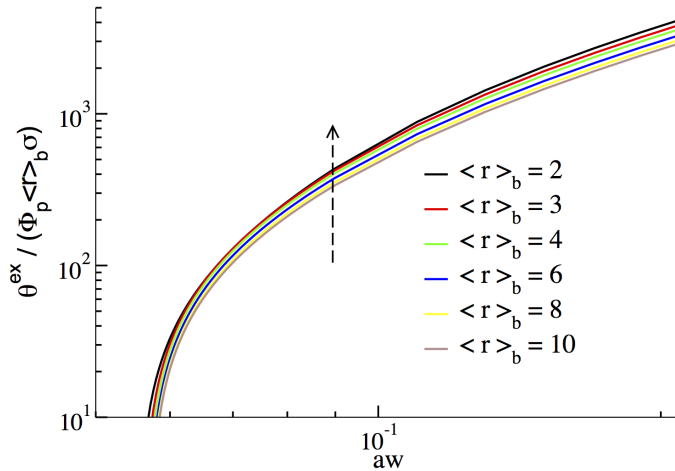


FIG. 6: Plot of the excess adsorption on the surface $\theta^{ex}/(\Phi_p \langle r \rangle_b \sigma)$ as a function of attraction strength on the surface, a_w , for different average lengths. The bound peptide density in the bulk $n^b(bulk)\sigma^3 = 10^{-3}$ and the arrow indicates the direction of decreasing $\langle r \rangle_b$.

In Fig. 7 and Fig. 8, we plot similar adsorption profiles, but at much smaller bulk peptide densities. This should have the effect of diminishing the steric effect. While showing similar behaviours to the adsorption profiles at higher bulk density, we do note the presence of an inflection point in these profiles suggesting a sudden (orders of magnitude) increase in the adsorbed peptide concentration at a particular value of a_w . We reiterate that this is not a

true phase transition, but reflects the adsorption transition that occurs in the ideal system – a ”soft transition”. Indeed, we see in Fig. 8 that the soft transition in the surface adsorption for $\langle r \rangle_b = 2$, occurs at a value of a_w , which is close to the estimated adsorption transition point in the ideal system, at the same average length. As expected, the soft transition also occurs at a smaller adsorption strength the larger is $\langle r \rangle_b$.

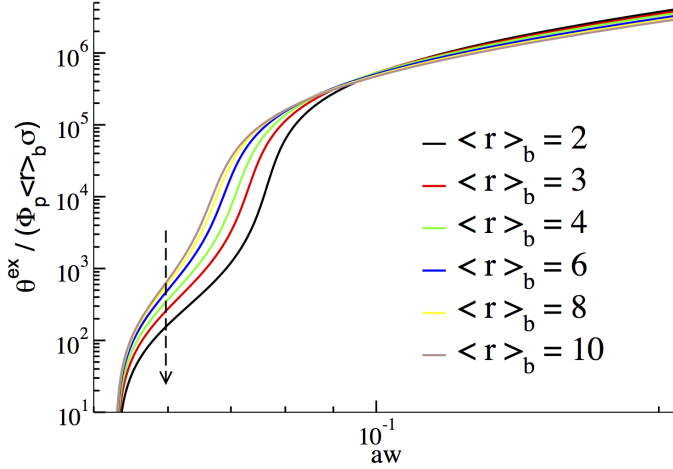


FIG. 7: Plot of the excess adsorption on the surface $\theta^{ex} / (\Phi_p \langle r \rangle_b \sigma)$ as a function of attraction strength on the surface, a_w , for different average lengths. The bound peptide density in the bulk $n^b(bulk)\sigma^3 = 10^{-6}$ and the arrow indicates the direction of decreasing $\langle r \rangle_b$.

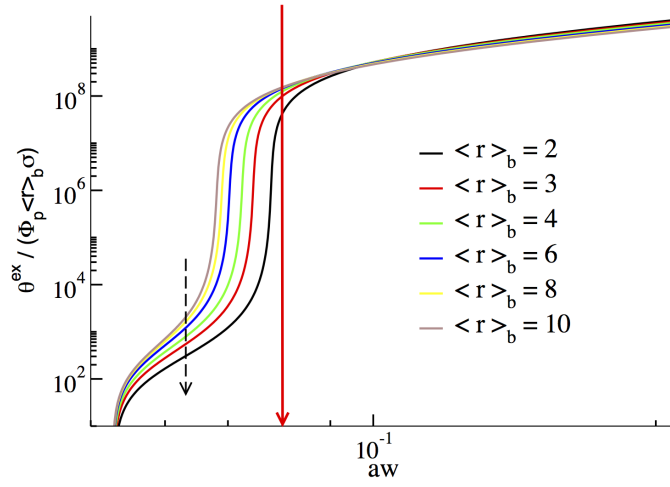


FIG. 8: Plot of the excess adsorption on the surface $\theta^{ex}/(\Phi_p \langle r \rangle_b \sigma)$ as a function of attraction strength on the surface, a_w , for different average lengths. The bound peptide density in the bulk $n^b(bulk)\sigma^3 = 10^{-9}$ and the dashed arrow indicates the direction of decreasing $\langle r \rangle_b$. The red solid arrow shows the point where the adsorption of ideal polymer on the surface goes to infinity for the case $\langle r \rangle_b = 2$.

C. Steric interactions - local theory

The non-local theory describes above is able to describe structuring in the density profiles of the adsorbed peptide filaments. However, at very high adsorption strengths, the iterative solutions of the PDFT become rather laborious. On the other hand, the *local* model may be a viable alternative approach, especially at lower adsorption strengths where the peptide density profiles are less structured.

In Figs. 9 and 10 we plot the bound peptide density profiles for the local model using the same set of parameters as those in Figs. 4 and 5. The local and non-local theories show good agreement at low values of a_w (compare Figs. 9 and 4). On the other hand, for large adsorption strengths (Fig. 5 and Fig. 10) there is qualitative disagreement, as expected. The local theory shows less structure and certainly no indication of the expected layering behaviour. However, the excess adsorption density profiles from the local model are similar to the results of the non-local model. That is, while the density profiles are qualitatively different, the integrated densities of both approaches give similar values.

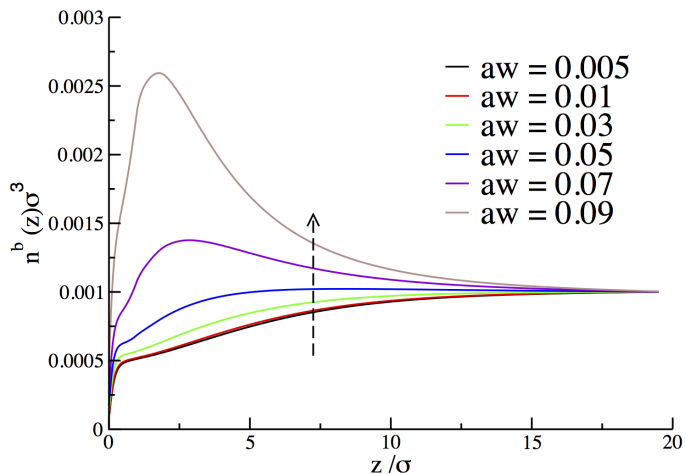


FIG. 9: Plot of $n^b(z)\sigma^3$ as a function of z/σ for polymer with hard sphere terms for increasing surface attraction and $n^b(bulk)\sigma^3 = 10^{-3}$. The arrow indicates the direction of increasing a_w .

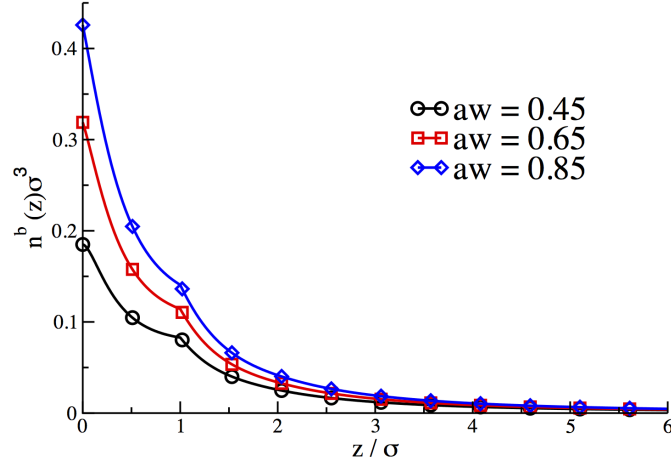


FIG. 10: Plot of $n^b(z)\sigma^3$ as a function of z/σ for polymer with hard sphere terms and larger attraction from the surface. The bound peptide density in the bulk $n^b(bulk)\sigma^3 = 10^{-3}$.

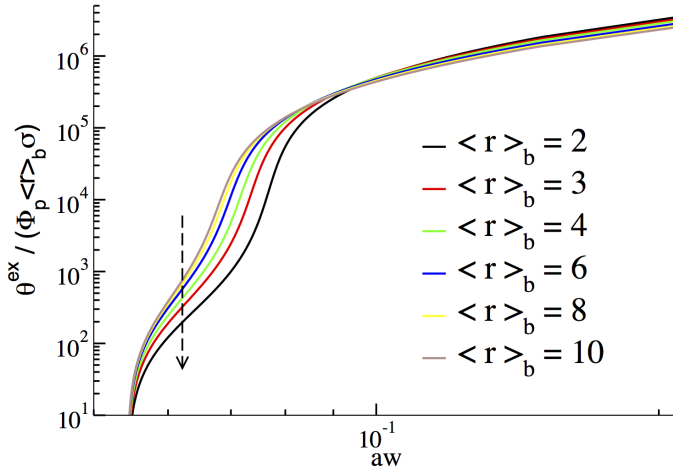


FIG. 11: Plot of the excess adsorption on the surface $\theta^{ex} / (\Phi_p \langle r \rangle_b \sigma)$ as a function of attraction strength on the surface, aw , for different average lengths. The bound peptide density in the bulk $n^b(bulk)\sigma^3 = 10^{-6}$ and the arrow indicates the direction of decreasing $\langle r \rangle_b$.

VI. CONCLUSION

In this work we have generalised the PDFT to treat living random copolymer systems. This theory was then applied to the problem of amyloid peptide adsorption onto surfaces at various degrees of adsorption attraction. We used the model of van Gestel and de Leeuw [25] for the $A\beta$ peptide, which is known to aggregate into peptide filaments, wherein the monomers consist of peptide conformers in either a β or disordered state. The former is able to form β sheets with neighbouring β conformers and build up long peptide filaments.

Our results show that the presence of an attractive surface is able to facilitate the formation of these filaments to an exceptional degree. The reason for this is an underlying second-order adsorption transition. This transition is seen in infinitely long polymer systems under Θ conditions, as exemplified in the work by de Gennes [17, 48], and later shown for polydispersed polymers [14, 49, 50]. We have shown that this transition is also exhibited in the generic amyloid model of van Gestel and de Leeuw, in the case of ideal peptides. When we allowed for steric interactions between the peptides, this adsorption transition was suppressed, due to the exclusion effect of peptides already adsorbed onto the surface. However, the peptide adsorption still clearly showed some remnant of the ideal fluid adsorption transition. There was an order of magnitude increase in the adsorption at a critical adsorption strength, which decreased for larger average filament length. The increase in the adsorbed peptide density corresponds to a significant increase in filament lengths adjacent to the surfaces. This work gives a mechanistic explanation to the experimental observations that surfaces are able to enhance the formation of amyloid fibrils [27–31]. Furthermore, the theory developed here can be further applied to many other systems, which display reversible bonding of co-monomers.

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