A self-consistent field study is presented on the design of active and passive targeting block copolymeric micelles. These micelles form in water by self-assembly of triblock copolymers with a hydrophilic middle block and two hydrophobic outer blocks. A minority amount of diblock copolymers with the same chemistry, is taken to co-assemble into these micelles. At the end of the hydrophilic block of the diblock copolymers a targeting moiety (TM) is present. Assuming that the rotation of the micelle towards the target is sufficiently fast, we can elaborate a single gradient cell model, wherein the micelle is in the center and the receptor (R) substrate exists on the outer plane of the spherical coordinate system.

The distribution function of the targeting moiety correspond to a Landau free energy with local minima and corresponding maxima. The lowest minimum, which is the ground state, shifts from within the micelle to the adsorbing state upon bringing the substrate closer to the micelle, implying a jump-like translocation of the targeting moiety. Equally deep minima represent the binodal of the phase transition, which is, due to the finite chain length, first-order like. The maximum in between the two relevant minima implies that there is an activation barrier for the targeting moiety to reach the receptor surface.

We localize the parameter space wherein the targeting moiety is (when the micelle is far from the target) preferably hidden in the stealthy hydrophilic corona of the micelle, which is desirable to avoid undesired immune responses, and still can jump out of the corona to reach the target quick enough, that is when the barrier height is sufficiently low. The latter requirement may be identified by a spinodal condition. We found that such hidden TMs can still establish jump-like TM-R contact at distances up to twice the corona size. The translocation transition will work best when the affinity of the TM for the core is avoided and when hydrophilic TMs are selected.

**keywords:** micelle, Scheutjens-Fleer Self-Consistent Field theory (SF-SCF), particle size prediction, active and passive targeting micelles, copolymers, targeting moiety receptor contact.

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### I. INTRODUCTION

Nanoparticles are nowadays used for pharmaceutical applications [1–4]. The drug delivery performance of such particles depends on control over particle size, drug loading and active targeting capability. One can use nanosized micellar structures formed by a combination of (different) amphiphilic molecules in a selective solvent. Nanoprecipitation enables the formation of self-assembled block copolymer spherical micelles, even for rather hydrophobic copolymers. Potent drugs are often rather hydrophobic ingredients for which polymeric micelles are promising carriers, with potential for controlled encapsulation of compounds at high loadings. Additionally, using polymeric micelles offers routes to control release, stability and bio-distribution of active agents in the body for both passive and active targeting [5–13]. Here we focus on water as the solvent and consider block copolymers with two apolar and one polar block, the so-called ABA blockcopolymers which readily form spherical flower-like micelles. To assure active targeting we propose to combine the triblock copolymers with AB diblocks with targeting moieties at the end of the hydrophilic block B. Within the spherical micelles the hydrophobic entities are collected in a compact core, whereas the water-soluble blocks remain hydrated and form a corona. The diblocks are designed in such a way that their B blocks are preferably located outside the hy-
hydrophobic core of the micelle. As hydrophobic blocks A we envision poly-(lactic-co-glycolic) acid (PLGA) and as hydrophilic block B polyethylene oxide (PEO). Although PEO is non-degradable it is non-toxic and can easily be removed from the body by the normal excretion (renal) pathways as long as the molar mass is below 20 kDa [14]. The hydrophobic part consists of PLGA, an FDA approved and well known biodegradable polymer used in commercially available drug delivery applications [4, 15]. In principle PEO and/or PLGA can be replaced by other hydrophilic and hydrophobic (co)polymers.

The goal is to obtain more fundamental insight in the behaviour of copolymers with targeting moieties within composite micelles. The method employed, the Scheutjens-Fleer self-consistent field (SF-SCF) theory [16–18], successfully used earlier to theoretically study the triblock copolymer micelle structure and stability [19, 20]. It was found that by implementing a model wherein segments are represented as amorphous beads, i.e. \( A_{60}B_{60}A_{60} \) (PLGA\(_{60}\)PEO\(_{60}\)PLGA\(_{60}\); 7.5-6.0-7.5 kDa), there exists a set of interaction parameters that leads to structural properties of micelles that compare favourably with the ones found experimentally using the solvent precipitation method [21]. Once such micelles have formed, we envision that the core becomes unresponsive, i.e. glassy, and this allows us to focus here exclusively on what happens in the molecularly quenched, but conformationally adaptive corona. Basically we take the core to be a solid particle (composed of units of type A; PLGA) of which the size is set equal to that found for the micelle cores. We graft both ends of a hydrophilic chain \( B_{60} \) (PEO; 6.0 kDa) onto the core so that a spherical brush is formed of looped chains. The grafting density of this brush is set equal to the aggregation number found for the self-assembled micelles. Next we consider that onto the same core there is one chain grafted by one end only, the AB (PLGA-PEO) diblocks leaving one free dangling chain end. We take the chemistry of this chain identical to that of the triblocks, only the length of the B (PEO) block of this minority chain is a free variable. The key is that the free end is given some different properties, consistent with the idea that this end is functionalized by a targeting moiety (TM). The focus of this paper is to understand the behaviour of the minority chain and in particular understand the whereabouts of the functional free end. In more detail our attention will be on the translocation transition of the minority chain end going jump-like from being inside the corona to outside the brush, a transition which is driven by the potential energy gain received when the TM is in contact with a receptor (R). In our simple cell model the receptor is expected to be present homogeneously along the surface that surrounds the central micelle.

Biodistribution of micelles in the human body is mainly dependant on their size, surface and corona structure. Micellar size control exploits passive targeting via the enhanced permeation and retention (EPR) effect [22–26]. For targeting purposes we focus on tumor cells and tissue as an example. Improving chemotherapy offers a major challenge in human health treatments. Of course other diseased tissues will demand different targeting moiety (TM) receptor (R) combinations. Especially for micellar accumulation in tumor tissues the size and surface structure is of crucial importance for passive targeting.

For active targeting one needs to incorporate moieties for specific targeting into or onto the micellar corona. Ideally targeting moieties are included that are specific for the targeted tissue. When the connection between targeting moiety and receptor is strong enough active targeting will be enabled. From the biological perspective there is a number of requirements. First of all the micelle needs to have the proper chemistry. It is known that polyethylene oxide micelles are stealthy (non interfering with the immune system) and have long blood circulation times [27]. Hence we take the interaction parameter for the \( B \) group with water accordingly. To avoid any undesired interaction with the immune system we believe that it is favourable to have the chain end well inside the micelle corona, that is under normal operation conditions, it is favourable to have the chain end well inside the micelle corona, that is under normal operation conditions, when the micelle is far from its target. This requirement can be implemented in two ways. In the first option we take the length of the minority chain to be less then half the length of the loops that form the bulk of the corona, i.e. \( N_B < 30 \). To go outside the corona will imply extra stretching of the minority chain which is entropically unfavourable. The second option is to give the free chain end an affinity for the core of the micelle. Typically this already occurs when the targeting moiety is hydrophobic. Then there is a natural tendency that the TM is associated to the core. In the adsorbed state of the TM to the corona is obviously inside the corona, even when the length of the minority chain exceeds that of the half-loop length. Experimentally, when the TM is hydrophobic, it may be locked inside the core and is subsequently unable to escape from it. Here we will ignore this scenario because we take the core to be composed of A-segments only (the core is a boundary condition in the current calculations). On top of the hydrophobic interaction we may introduce some extra surface affinity, e.g. due to some specific interactions. Of course this will complicate our analysis because there will be a free energy barrier associated with the detachment of the endgroup from the core and the time limiting step for the translocation transition may well be associated with the desorption process, rather than being associated to the entropic stretching towards the adsorbing surface itself.

The design, manufacturing and characterization of ABA block copolymer micelles composed of rather hydrophobic copolymers was reported previously [19–21]. It was demonstrated that tuning the size and loading can be achieved by using triblock copolymers with a particular chain length combined with active ingredients. The synthesis and incorporation of targeting moieties onto existing particles is difficult and tedious. In most cases the targeting function on a nanoparticle/micelle
is established after its formation. Since most of these processes demand surface chemistry instead of physical interactions, a purification step is mandatory to remove reactants [28–32]. To omit the post processing and purification steps we propose a single micellar processing method. This allows incorporation of the targeting moieties, present on the dillblocs, from the start of the micellar production process using the nanoprecipitation method. It is noted our approach and the results can also be applied towards targeting applications using polymer coated nanoparticles.

We first give elementary background information on the modeling method, focusing on the main approximations. We then provide detailed information on the model used and discuss the relevant parameters. We present the structure of the polymeric micelle that is used to further study the escape or translocation transition of the minority chain. In somewhat more detail we will subsequently discuss how we are going to analyse the translocation transition of the TM-R contact. The main results are collected in diagrams of state wherein the binodal and spinodal curves are collected. These diagrams facilitate the search for the most optimal properties of the minority chain in a composite micelle. In our discussion and conclusions we sum up our theoretical modelling results with regard to the design of an active targeting capacity for composite micelles.

II. THEORY

This section contains two major parts. First focus is on outlining the SF-SCF theory. We explain the main approximations of the modelling in combination with the model that is used for the copolymer self-assembly. For more detailed information we refer to [19, 20]. Subsequently, the micelle is presented that is selected as a representative case in some detail and reproduce a result from a previous study [20] for ease of reference. Next, we elaborate on the model used for the remainder of this paper. The cores of the micelles are molecularly quenched, implying that the aggregation numbers and core structure are frozen in. Important is that the micelles remain responsive in the micelle corona for which the chains can conformationally rearrange. In the second section we elaborate on the use of the Landau free energy (see [33]) by elaborating on a specific example, and explain in detail the physics that are accounted for. In this section attention is being paid to definitions of the binodal and spinodal from the SF-SCF results. Finally, the relevant SF-SCF parameters are discussed which will be investigated on their influence on TM-R contact.

A. SF-SCF theory

Making use of the mean field approximation, and more specifically the Bragg-Williams approximation (more about this below) allows to formulate for a system a free energy in terms of two conjugate profiles, namely the measurable volume fraction (dimensionless concentrations) \( \varphi(r) \) and complementary segment potential \( u(r) \) distributions. In a way these potentials are external potentials because we use them to obtain statistical weights, the so-called Boltzmann weights as in a barometric height equation \( G(r) = \exp(-u(r)) \). Here and below all energy quantities are made dimensionless by normalising them with the thermal energy \( k_B T \). The weights are not fixed, but the segment potentials appear to be a function of the volume fractions. The functionality follows uniquely from the free energy optimisation. As a result the segment potential take the interaction of a given segment with its surroundings into account. These interactions are parametrized by Flory-Huggins interaction parameters \( \chi_{X-Y} \) wherein both X and Y are segment (or solvent) types. A positive value means that the XY contacts are less favourable than the average of XX and YY contact. Hence a sufficiently large positive value implies segregation. Low values or negative values are needed for proper miscibility.

Interestingly, not only do the potentials depend on the volume fractions, the inverse is also true: the volume fractions are a function of the segment potentials. To implement this dependence, it is necessary to invoke a chain model. Here the freely jointed chain model is used, which guarantees that neighboring segments of the chain are at a distance of a bond length. However, as no further through-bond correlations are imposed a chain can also fold back on previously occupied places. Let us next focus on a particular conformation \( c \) of the chain, completely specified by the coordinates of the individual segments. This conformation is found to have a particular potential energy \( u_c \), which is computed by the sum over the segment potentials felt by the consecutive segments along the contour of conformation \( c \). The statistical weight of this conformation is then again given by a Boltzmann weight, \( G_c = \exp(-u_c) \). Such weight is found for all possible and allowed conformations. With these statistical weights one can construct the overall volume fraction distribution. Of course this requires a sum over the contributions of all possible and allowed conformations. As the total number of possible conformations is very large indeed, these sums suggest an insurmountably large job. Fortunately there exists an elegant propagator method that copes with it efficiently, in a computation time which is linearly proportional to the number of segments in the chain (not shown).

Summarizing, characteristic for the SCF method we have

\[
\varphi_i[u] \leftrightarrow u_i[\varphi].
\]  

In words, the left hand side of this equation says that
the volume fractions can be computed from the potentials and the right hand side says the opposite. In the case that the set of potentials and volume fractions is consistent, that is, that the potentials both follow from and determine the same volume fractions and vice versa, we refer to the solution being self-consistent. There is a pitfall, namely as specified thus for there are many SCF solutions to the equations. That is why one additional requirement is necessary to make the solution unique. This additional requirement specifies the use of an (in)compressibility relation. Here we opt the system to be incompressible and therefore we impose

$$\sum_X \phi_X(r) = 1$$  \hspace{1cm} (2)

for each coordinate \(r\).

In very few cases it is possible to solve the self-consistent field solution analytically. It is of no surprise that the self-assembly of copolymers into spherical micelles is not one of these rare cases. As a result we have to implement the equations into a computer model and solve for the fixed point numerically. Invariably, one needs to discretize the equations somehow. Here we follow the SCF method of Scheutjens and Fleer (SF-SCF) and make use of lattice of sites. The characteristic length of a lattice site is taken equal to the bond length, so that one polymer segment exactly fits into a lattice site. Solvent molecules are taken to have the same volume as a specific polymer segment.

For many problems one can recognize some sort of symmetry element. For example in spherical micelles we can easily imagine that the relevant gradients in polymer densities occur in the radial direction and that the density fluctuations in a shell of lattice sites with equal distance to the center are very small. This motivates us to reduce the three-dimensional system and implement this in a one-gradient spherical geometry. Then lattice layers are numbered starting from the center \(r = 1, 2, \ldots, M\). Naturally, the number of lattice sites \(L(r)\) in layer \(r\) scales as \(L(r) \propto r^2\). By ignoring the density fluctuations in the layer (mean field approximation) we can implement the volume fraction \(\phi_X(r) = n_X(r)/L(r)\), wherein \(n_X(r)\) is the number of segments of component \(X\) in layer \(r\). At the upper boundary at \(r = M\) typically reflecting boundary conditions apply. This is implemented by forcing all density gradients to be zero at this boundary, i.e., \(\phi_X(M + 1) = \phi_X(M)\). Usually the value of \(M\) is taken very large, far from the micelle, which is positioned at the center of the spherical coordinate system, where the density gradients have vanished (bulk). Then these reflecting boundary conditions are inconsequential for any physical property of the system.

Below we consider a spherical ‘micelle’ in the vicinity of a surface. This typically cannot be captured in a spherical geometry. Instead one might be tempted to use a two-gradient cylindrical coordinate system. Below it is however shown that the problem of interest can be studied using a single gradient spherical geometry. More specifically, we are going to assume that the rotational diffusion of the micelle is quick enough so that the probe will find the receptor even when some rotation of the micelle is needed. Then having a surface in all directions around the micelle (as is explicitly implemented) is a reasonable approximation. This idea is realized by imposing an impenetrable boundary at layer \(r = M + 1\), that is, at layer \(r = M + 1\) the volume fraction of a segment with type \(R\) is unity. Segments with type \(X\) feel this boundary when they sit in layer \(z = M\) through the interaction parameter \(\chi_{X-R}\). Also the solvent \(W\) has an interaction with this surface, \(\chi_{W-R}\) and typically segments may adsorb onto the surface only when a solvent molecule is displaced from it, hence micelle adsorption is expected only when \(\Delta \chi_R \equiv \chi_{X-R} - \chi_{W-R} < 0\), otherwise the solvent is preferentially adsorbed at the surface. It is well known that polymer chains experience conformational entropy losses when they are directly next to an impenetrable wall, the reason for this is that the orientation of bonds is hindered as these cannot enter into the solid phase. To compensate for this, it is necessary that \(\Delta \chi_R < 0\), for the segment \(X\) (part of a chain) to adsorb, where in good approximation \(\chi_{critical} = -1\) for typical segments in a polymer chain. The critical adsorption energy for end-segments is expected to be less negative as these segments have just one bond connected to them. The critical adsorption is also a function of the solvent quality. To understand this, one should realize that a segment next to the surface cannot interact with the solvent in all directions. Hence it can avoid one contact with the solvent and thus there is an increased tendency to be next to the (receptor) surface. Below the affinity of the probe for the (receptor) surface is implemented using the parameter \(\chi_{TM-R}\). In our approach it is assumed that a large excess of receptors is available. Several authors have studied the effect of the availability of receptors and we refer to their papers for interested readers [34–37].

In the SF-SCF method the molecules are discretized, they are taken to be composed of segments numbered \(s = 1, 2, \ldots, N\). We refer to \(N\) as the chain length, but possibly the degree of polymerization is a better term for it. We do not take any structural features on the segment level into account. However, we do allow for copolymer type of interactions, e.g. one segment is hydrophobic and the other is hydrophilic. We do this by specifying the Flory-Huggins interaction parameters for each segment type accordingly (see section II C).

1. The molecular model and self-assembly

The study of the self-assembly of copolymers into, e.g., thermodynamically equilibrated spherical micelles is a key application of the Scheutjens-Fleer self-consistent field (SF-SCF) theory. In previous studies [19, 20] we considered the formation of spherical micelles composed of \(A_{60}B_{60}A_{60}\) where \(A_{60}\) (7.5 kDa) is the hy-
drophobic block mimicking PLGA and B60 (6.0 kDa) the hydrophilic block representing PEO (also called PEG, polyethyleneglycol).

Let us now formulate a key property of the molecular model. The set of parameters should result in micelles wherefore the core and corona sizes are of the same order of magnitude. Even though the topological stability requires the size of the core to be less than that of the corona, as explained, the dynamic process by which the micelles form is more likely characterized by the situation that the micelle corona is somewhat smaller than that of the core. We have opted for a driving force for micellisation using a modest value $\chi_{\text{LGA}-\text{H}_2\text{O}} = 1.6$, whereas the solvent quality for PEO is marginal: $\chi_{\text{EO}-\text{H}_2\text{O}} = 0.4$. This value ensures that the corona is well-solvated and the pressure in the brush provides the stopping mechanism for the self-assembly of the micelles. The spatial segregation of A segments in the core and the B segments in the corona is improved by a repulsion between these segments. Here we have used $\chi_{\text{LGA}-\text{EO}} = 1.0$ for simplicity. The justification of this set that it largely obeys with our requirements. We stress that small modifications of the parameter set do not perceptibly affect the results.

In Fig. 1 (a) the micelle structure, wherein the radial volume fraction profiles for the polar segments, the apolar segments and the solvent molecules is given, here it is observed that the core has approximately a homogeneous density of polymer. The small decrease of density towards the center of the core is attributed to an inhomogeneous stretching of the corona chains, being largest near the core-corona interface (where they then pack a bit more efficient). The solvent in the core is not extremely low, which is consistent with the relatively low value for the $\chi_{\text{LGA}-\text{H}_2\text{O}}$ that was adopted to mimic the assembly at the quench conditions. The corona has a much lower density, as it is well solvated. The profile is quasi parabolic, and the height (dimension) of this brush is expected to scale linearly with the length of the B block.

Inspection reveals that the core radius, which in this case is approximately 20 lattice units, is slightly larger than that of the corona. The latter may be estimated from the hydrodynamic diameter of the micelle which is found to be 56 lattice units (45 nm). This is consistent with one of the targets that were used for the molecular model. The overall dimension of the micelle is in good agreement with the micelles found in the experimental condition. From the modelling point of view the micelles are stable. For example we have selected a micelle with a grand potential (work of micelle formation) $\Omega = 10 k_BT$. This value is thought to be compensated by translational entropy of the micelle, and thus represents the situation that the micelles are far apart (dilute regime). Thermodynamic stability requires that the slope $\partial \Omega / \partial g$ is negative, which was shown to be the case in a previous study [19, 20]. The aggregation number, that is the number of tri-block copolymers in the micelle is predicted to be $g = 237$. Again the order of magnitude is consistent with experimental data. We refer that a brush of loops with chains of length $N_B = 60$ is usually seen as a brush composed of tails of length $N_B = 30$ with double grafting density. We have checked that this is a good approximation also in this case (result not shown).

In the following we will use the micelle presented above and analyse the behaviour of a minority chain that is added to this micelle. The distortion of the entire micelle by the minority chain is accounted for explicitly.
The analysis is facilitated when the micelle is replaced by a simpler structure. Considering the sharp interface between the core and the corona, we argue that it is possible to replace the core by a solid particle and replace the corona by a set of polymers that are anchored by both ends to this solid particle. In Fig. 1 (b) we present the structure of a brush of loops connected to a spherical particle. The parameters are chosen such as to resemble the corona of the micelle presented in Fig. 1, that is, the number of grafted ‘loops’ is equal to the aggregation number $g$, and the solvent quality is again set to $\chi_{EO-H_2O} = 0.4$. The differences in radial structure of Fig. 1 (a) and (b) are minor which proofs that the model of Fig. 1 (b) is sufficiently accurate to mimic a triblock copolymer micelle for our purpose as used below. The most significant differences between the two radial profiles occur just next to the ‘core’-corona interface. As explained above the entropic penalty for chains next to a sharp interface results in a small depletion of polymers and a small adsorption of solvent. In the micelle the core corona interface is less sharp and then the latter effects do not occur. One can easily correct for this entropy loss by adding an adsorption affinity of the corona chains for the core. This is not implemented here.

2. A minority chain within the corona of the micelle

Following the line of arguments we take the corona structure presented in Fig. 1 (b) and admix in this structure one minority chain with a structure $A_1B_{N_B}TM_1$. It was verified that a few minority chains do not strongly influence the colloidal stability of the micelle. The focus here is on the radial profile of a single minority chain inside the corona made of $A_1B_{N_B}A_1$. More specifically our interest is in the profile of the end-segment referred to as TM. In Fig. 2 we present a number of radial volume fraction profiles of the TM segment in semi-logarithmic coordinates. One of the profiles, that is for $N_B = 30$, is dotted. This case represents a mimic of the majority corona interface is less sharp and then the latter effects do not occur. One can easily correct for this entropy loss by adding an adsorption affinity of the corona chains for the core.

at the core surface. This result is true for an ideal TM, which is small (similar to an A-segment) and for the case that the water has the same solvent quality for the TM as the tether $A$. We are interested in parameters that deviate from this ideal situation and then there are discontinuities, meaning that there is a minor jump-like transition from the TM being inside to being outside the corona upon, e.g., an increase of the length of the minority chain.

Continuing with the ideal TM case, let us now consider the presence of a surface (receptor) at the upper boundary of the spherical coordinate system, that is at $r = M + 1$. Below we refer to the position of the receptor by the distance $\Delta r \equiv (M - R_b)$, wherein $M - R_b$ is the distance of the receptor from the hydrodynamic radius of the micelle in lattice units. Obviously, as long as an adsorbing receptor surface is present for distances larger than the chain length ($M - R > N_B$), the probe chain cannot reach this receptor surface and the end-point distribution is unaffected. However, when the receptor is in close proximity, the end of the probe can reach the receptor. When the end has a significant affinity for the receptor, we expect that the end segment, that is the targeting moiety (TM), is able to reach and adsorb onto the receptors. By doing so, the probability for the TM to be near the surface will dramatically increase as compared to the value at the same coordinate in the absence of the substrate. A cartoon of this situation is given in Fig. 3 (b), which mimics the situation depicted in Fig. 3 (a). In this figure the end-point sits at the substrate. In reality the TM is only located at the receptor surface with a given probability smaller than unity. Insights into binding of end grafted polymers to flat surfaces was
obtained by performing computer simulations [38]. This case was also studied theoretically [39]. Our interest is in the probability distribution of the end point (receptor), which in fact is proportional to the radial volume fraction profile. The end-point distribution may potentially have two maxima, namely one in/around the corona (we will call this the central maximum) and one next to the adsorbing surface (we call this the distal maximum) and two minima, namely between the core and the periphery of the corona (the proximal minimum), and one between the adsorbing surface and the periphery of the corona (the distal minimum).

B. Landau free energy and a short case study

The free energy of the system $F$ in units of $k_B T$ is found by $F = -\ln Q$, where $Q$ is the canonical partition function. In a mean field theory, we can decompose this partition function into so-called single molecule sub-partition functions $q_i$,

$$Q = \prod_i q_i^{n_i} / n_i!$$

where $n_i$ is the number of molecules of type $i$. Following the line of arguments, it is natural to take a closer look at the minority chain, while assuming that the other sub-partition functions are invariant upon changes in the conformational properties of the minority chain, e.g., when it binds onto a nearby receptor. Of course for this to be true we should insist on the case that the receptor surface remains outside the corona of the micelle in all cases.

The sub-partition function for the minority chain in principle should contain the statistical weights of all possible and allowed conformations. The evaluation of this partition function is simplified because the first segment is strictly positioned to be next to the core surface. In practice the propagator formalism is used here to generate the partition function. In this formalism there are distribution functions $G(r,s|R + 1,1)$ that specify the statistical weight of having segment $s$ at coordinate $r$, under the constraint that the first segment $s = 1$ is at coordinate $r = R + 1$, that is next to the core. In the propagator equation this distribution function is computed starting with $s = 1$, and ending with segment $s = N$ giving $G(r,N|R + 1,1)$. Interestingly this end point distribution function can be used to directly compute the volume fraction profile of the free end, that is, $\varphi(r,N) \propto G(r,N|R + 1,1)$. The proportionality constant is $1/q$, wherein the single chain partition function $q$ is found by summing this quantity over all available coordinates $r$

$$q = \sum_r L(r)G(r,N|R + 1,1)$$

Inspired by this relation we can identify $G(r',N|R + 1,1)$ as a positional sub-partition function of the probe chain, which starts (per definition) with segment $s = 1$ at $r = R + 1$ and ends with segment $s = N$ at coordinate $r'$. The free energy associated with this positional sub-partition function is called the Landau free energy $F_0(r)$ [40–42], which in units of $k_B T$ is given by

$$F_0(r) = -\ln G(r,N|R + 1,1) = \ln q - \ln \varphi(r,N)$$

The constant $\ln q$ can be absorbed into the Landau free energy

![FIG. 3: Schematic two-dimensional representation of (upper panel) a micelle with a minority chain adsorbing with a targeting moiety (TM) to a receptor (R) site on an external planar substrate (e.g. a cell wall with receptor). Lower panel: A central micelle surrounded by a spherical 'substrate' as considered in the cell model; the TM of the minority chain adsorbed on this substrate, which is expected to be covered by receptors (not indicated). The core of the micelle is red, the corona blue (a few corona chains -loops- are indicated). The minority chain is green and has a TM (represented by TM).]
energy. Here and below we will use \( F(r) \equiv F_0(r) - \ln q \). Hence the Landau free energy can directly be computed from the radial volume fraction profile of the end point of the minority chain. In the current context the position of the free end \( r \) is often referred to as the order parameter.

In practice a targeting moiety (TM) consists of a somewhat larger fragment than an ethylene oxide segment. We can mimic this by taking a minority chain with the following architecture: \( A_1B_{25}X(TM)_{N_{TM}} \), with \( N_{TM} > 1 \). We may subsequently generalize the Landau formalism by relating the Landau energy to the volume fraction distribution of all the TM-segments, that is, \( F(r) = -\ln \varphi_{TM}(r) \).

At this stage it is of interest to discuss an example of how we are going to use this Landau free energy. For this we use the minority (probe) chain \( A_1B_{25}TM_5 \). The segments TM are taken similar to that of B, with the exception of the affinity of the TM for the receptor surface \( \chi_{TM-R} \). While all affinities \( \chi_{R} = 0 \), the (strong) affinity for the targeting moiety for the receptor is reflected in a negative value for this parameter. Landau free energy curves are presented in Fig. 4. Note that in these computations an excess of multivalent ligands are considered, which is beneficial for targeting. See [34, 35] for the case of limited availability of receptors. Without losing generality one can add a constant to the Landau function. Here we choose to shift each curve such that all Landau functions attain a zero value at the core side. For illustration purposes we set the receptor surface very close to the edge of the corona, namely at \( r_R = 25.6 \) nm in Fig. 4 (a) and slightly further outward, that is \( r_R = 28.0 \) nm in Fig. 4 (b).

As can be seen in Fig. 4, as long as \( \chi_{TM-R} = 0 \) the Landau function has one central minimum and two maxima. With respect to the core, we have a proximal maximum at \( F_{\text{max}} = 0 \) and a distal maximum at the receptor surface. Of course this central minimum corresponds to the central maximum in the volume fraction profile (see Fig. 2). With increasing affinity for the receptor a new (distal) minimum develops, that is, near the receptor surface. The distal maximum is naturally moved to lower values of \( r \). For a particular value of \( \chi_{TM-R} \) the depths of the central and the distal minimum are the same. This occurs for \( \chi_{TM-R} \approx -2 \) in Fig. 4 (a) and \( \chi_{TM-R} \approx -3 \) for Fig. 4 (b). Using state transition terminology we can identify the equal depth condition as the binodal. The distal maximum in between the central and distal minimum is identified by the activation barrier that needs to be overcome by the TM to reach the receptor. At the binodal the height of the barrier \( U \) does not depend on which minimum is used to measure the height. When \( \chi_{TM-R} < \chi_{TM-R}^* \) the height as measured from the central minimum is lower than that measured from the distal minimum. Below, when we discuss the height of the barrier, we will always measure this height taking the central minimum as the reference. The physical origin of the barrier is clear. Before the TM can reach the receptor, it has to stretch even further than its naturally stretched conformation in the corona. This stretching costs entropy and hence the free energy increases. The lowest minimum in \( F(r) \) corresponds to the ground state. Taking the affinity for the receptor as the control variable it is clear that at \( \chi_{TM-R} = \chi_{TM-R}^* \), the ground state is degenerate. For lower affinities the lowest free energy is when the TM is inside the brush, whereas at larger affinities the ground state is when the the TM is at the receptor. For successful targeting the latter is required.

In all cases the height of the barrier \( U \) decreases when \( \chi_{TM-R} \) becomes more negative. In this case the probability of finding the TM next to the receptor increases more and more and eventually the height \( U = 0 \). This condition is identified by the spinodal of the translocation.

**Fig. 4**: The dimensionless Landau free energy \( F(r) \) (in units of \( k_BT \)), where \( r \) is the distance to the center of the core for a probe chain \( A_1B_{25}TM_5 \) in lattice site units for various values of the affinity of the TM for the receptor \( \chi_{TM-R} \) as indicated, for the position of the receptor surface. (a): Position of the receptor surface \( r = 32 \). (b): Position of the receptor surface \( r = 35 \). The Landau free energy is normalized such that \( F(16.8) = 0 \). Note that in panel (a) the curves for \( r < 27 \) overlap. The same happens in panel (b) for \( r < 30 \). The vertical (dashed black) line represents the upper limit of the overlap. The same happens in panel (b) for \( r < 30 \). The vertical (dashed black) line represents the upper limit of the cell and where the receptor surface is present.
transition. In Fig. 4 (a) this happens for $\chi_{TM-R}$ such that $F_{\chi_{TM-LGA}}$ for various values of the affinity of the TM for the core (composed of units A) $\chi_{TM-LGA}$ as indicated, for the position of the receptor surface (dashed black line), $r_R = 35$ and $\chi_{TM-R} = -3$. The Landau free energy is normalized such that $F(r_R) = 0$. Note that all curves overlap for $r > 25$.

In Fig. 4 (a) and (b) can be used to understand that $\chi_{TM-R}$ decreases with $r_R$, and that the height of the barrier at the binodal $U^*$ increases with $r_R$. Also the spinodal $\chi_{TM-R}^{**}$ decreases strongly with $r_R$. Clearly, for the minority chain to be a good targeting moiety we need $r_R$ to be larger than the hydrodynamic radius of the micelle, and the affinity for the target should be $\chi_{TM-R} < \chi_{TM-R}^{**}$. Meanwhile, the barrier $U$ should be not too high. Of course it is not necessary that the barrier vanishes (spinodal condition) completely. We expect that when $U \approx 3 k_B T$ the barrier can easily be crossed and therefore we will monitor besides the binodal and the spinodal also the $U = 3$ situation. Obviously the latter is only relevant when the barrier at the binodal $U^* > 3 k_B T$.

Before advancing to the results section we need to consider one more complication, namely when the TM has an affinity for the core. In this case it is more natural to normalize the Landau free energy so that the value at the receptor surface is zero. In Fig. 5 we show results for the Landau function for which the receptor substrate is set to $r_R = 35$, and the TM has, in addition to a mild affinity for the receptor, $\chi_{TM-R} = -3$ (close to the binodal of the translocation transition), some extra affinity of the TM for the core. A more negative value for $\chi_{TM-LGA}$ implies stronger adsorption of the TM onto the surface of the core. The curve for $\chi_{TM-LGA} = 1$ also given in Fig. 4 and is here reproduced for comparison reasons. When $\chi_{TM-LGA} < 1$ a proximal minimum develops in the Landau free energy and the natural proximal maximum is shifted to a position in between the proximal minimum and the central minimum. Now the situation is significantly more complex: there are three minima, the proximal, central and distal minimum (compared to the core) and two maxima (proximal and distal). Again we may identify the condition that the proximal and central minima are equally deep. This binodal corresponds to the detachment transition of the TM from the surface and occurs for $\chi_{TM-LGA}^{**} \approx 0$. We may also identify a spinodal for the detachment transition. In this case $\chi_{TM-LGA}^{**} \approx -6$ and the barrier between the proximal and central minimum vanishes. When $\chi_{TM-LGA} < \chi_{TM-LGA}^{**}$ the proximal maximum and the central minimum are gone and we are left with two minima, namely a proximal and a distal one with one maximum in between. When the three minima are equally deep, that is when $\chi_{TM-LGA} = \chi_{TM-LGA}^{**}$ and $\chi_{TM-R} = \chi_{TM-R}^{**}$, we have so-called triple point conditions as three 'phases' (types of conformations of the probe chain) can coexist.

From this result we can already extract our first design-rule for successfully targeting a receptor. We should avoid a strong affinity of the TM for the substrate. Indeed, it is not expected that the receptor can successfully fish for the TM when it is strongly attached to the core. Of course as long as the affinity of the TM for the receptor is much higher than that for the core, we should expect that at a sufficient close proximity of the receptor to the micelle, the TM-R contact is the ground state. However the energy barrier for this case will always be very high and the translocation transition will be a very slow one. That is why, in the following we will restrict ourselves to the case that the TM has a small repulsion to the core, which technically is equivalent with the situation that there is no affinity with the core. This does not mean that the TM cannot adsorb onto the cornea. As explained, also when the TM is not very soluble with water, there may be an induced adsorption energy and corresponding high concentration of the TM next to the core. As a result the Landau free energy will have a primary minimum and when this minimum is deeper than the central one, this will be used to measure the height of the barrier $U^*$ for obvious reasons.

Below the focus is on finding conditions so that the ground state is the distal minimum, while the central minimum is at a position lower than the hydrodynamic radius of the micelle. Then the minority chain will try to reach the receptor starting from a 'hidden' (for the immune system) position. However, the energy barrier $U$ that needs to be overcome to reach the receptor may
well be so large that the translocation of the TM towards the receptor is a rare event. The idea is then to monitor the $U = 3 k_B T$ condition (as measured from the micelle core/corona). The numerical value is an *ad hoc* estimate below which the receptor is expected to be found fast enough and above which this is too slow. Results can be collected in so-called state diagrams. Such diagrams collect the binodal and spinodal points when one parameter (e.g. the length of the minority chain) is varied and the transition is triggered by some control parameter (e.g. $r_R$). The binodal curve(s) in such state diagram give the important information regarding the translocation and/or detachment transitions. The spinodals give information on where the respective barriers vanish. The $U = 3 (k_B T)$ curve will be presented for discussion purposes only.

### C. SF-SCF parameters

Similarly as above, we base our analysis on the model derived from the spherical micelle composed of PLGA$_{60}$PEO$_{60}$PLGA$_{60}$ chains (as shown previously by [19, 20]). Again, the core was replaced by a spherical particle composed of PLGA segments with radius $R = 16$ nm, decorated by 237 chains with length 60 grafted on both ends to the core. These chains are assumed to be composed of PEO and this was modelled by the solvent quality parameter $\chi_{EO-H_{2}O} = 0.4$. We used minority chains with lengths $N_{R} = 5, 10, 15, 20, 25, 30, 35, 40, 60$ and 120, composed of EO units that are end-grafted onto the solid particle, while they have a targeting moiety at their free ends. There are three types of interaction parameters connected to the TM: (i) the affinity of the TM for the core. As argued above we will avoid large affinities of the TM for the core and here take $\chi_{TM-LGA} = 1.0$ (recall $\chi_{LGA-H_{2}O} = 1.6$), (ii) that for the receptor $\chi_{TM-R} = -3, -6, -12$ and $-18$ (recall $\chi_{R-H_{2}O} = 0$) and (iii) the solvent quality $\chi_{TM-H_{2}O} = 0.1, 0.4, 1.0$ and 3.0. On top of this the length of the TM (the volume of the TM or the repeating TM units) was varied $N_{TM} = 1, 3, 5$ and 10. Without mentioned otherwise just one minority chain was used.

### III. RESULTS AND DISCUSSION

The relevance of several parameters for the translocation transition of the targeting moiety is conveniently presented in state diagrams. We will present a representative set of these in the first part of this section. After that we will zoom in onto the optimized system for the use of polymer micelles as a targeting device for medical (drug delivery) applications.

#### A. The default state diagram

Below we adopt the convention to define the position of the receptor surface with respect to the hydrodynamic radius of the micelle, that is we introduce $\Delta r = r_R - (D_h)/2$. Hence, $\Delta r = 0$ means that the receptor is ‘touching’ the micelle corona layer. Negative values of the receptor distance $\Delta r < 0$ (overlap of corona and receptor surface) were disregarded, whereas positive values are of interest (the larger the better). We present state diagrams (cf. Fig. 6 (a)) in the coordinates (i) $N_{R}$, that is the length of the hydrophilic block of the minority chain (y-axis), and (ii) $\Delta r$, which is the distance of the receptor to the micelle surface on the x-axis. It is noted that the following conventions are adopted: solid curves represent the binodal condition and dashed curves represent the spinodal. Let us, for completeness, mention how to interpret such state diagram. When for given $N_{R}$, the TM is far from the micelle we are to the right of the binodal, and the central minimum is the ground state. Upon reducing $\Delta r$ we approach the binodal-curve at $\Delta r = \Delta r^*$. At this point we expect that the TM can thermodynamically reach the receptor 50% of the time, but this is an activated process as a barrier with height $U^*$ needs to be overcome. When the receptor comes even closer to the micelle, the TM-R state is the ground state and the energy barrier is gradually reduced. When the dashed spinodal curve is crossed, at $\Delta r = \Delta r^{**}$, every attempt of the TM to reach the receptor is expected to be successful as the energy barrier is gone. The height of the energy barrier $U^*$ at the binodal as a function of the chain length $N_{R}$ at the binodal is additionally presented in panel b which accompanies the state diagram, i.e., Fig. 6 (b). Here we have adopted to present the dependence with a solid curve when the TM is sufficiently short, so that in the absence of the receptor the TM is hidden inside the micelle corona. For longer chains this is no longer the case and part of the chain including the TM is outside the corona (dotted curves). In this regime we have used a dashed curve. As long as this energy barrier is sufficiently low, we choose a value of $3 k_B T$, the binodal is the most relevant curve in the state diagram, as it demarcates the point from whereon the translocation can effectively take place. However, when this energy barrier is much higher, a point closer to the spinodal is more relevant because of kinetic reasons the binodal is not noticed. At the spinodal translocation occurs spontaneously. This condition is indicated by a dotted curve in the state diagram, corresponding to $U = 3 k_B T$.

We start with a basic/default state diagram shown in Fig. 6. It is noted that the chain length $N_{R}$ of the B block should always be compared to the (hydrophilic) middle block length of the triblock, in this case 60. Here we have opted for a TM which is 3 segments long and a relatively low value for the affinity for the receptor of $\chi_{TM-R} = -3$. Again we have taken the situation that the minority chain has a vanishing affinity for the core. The current state diagram is representative for all cases that
the TM is repelled by the core or has a very negligible attraction. For a large affinity of the TM for the core the state diagram alters dramatically (not shown). In this case the energy barrier at the binodal is very small and the curve for $U = 3 k_B T$ is irrelevant. Inspection of the state diagrams shows that with increasing length of the minority chain, the capture distances (binodal-solid curve) $\Delta r^*$ as well as the spinodal conditions $\Delta r^{**}$ (dashed curves) increases. There exists a minimum value for $N_B$ below which the binodal, and spinodal distances are becoming negative, meaning that the minority chain is too short and the receptor has to penetrate into the micelle before the TM can capture it. The binodal and spinodal curves are not plotted for longer chains than $N_B = 120$ either.

For large values of $N_B$ the TM is outside the micelle (see dotted curve in Fig. 6 (b)). In this regime the minority chains have a flower-like conformation: they have a strongly stretched stem and a coil-like crown. The crown is outside the micelle and this crown can be used to stretch towards the receptor. For these long chain lengths the binodal and spinodal distances grow linearly with the length of the minority chain. This indicates that the chain has to stretch proportional to the chain length to reach the receptor. In this limit the stretching free energy (conformational entropy loss) is expected to be proportional to the chain length $N_B$ as well and this is in good agreement with the result of Fig. 6 (b) for large values of $N_B$. Hence the barrier $U^*$ has an entropic origin. When the TM extends towards the receptor the chain has a reduced conformational entropy. The position of the barrier is invariably close to the receptor surface, because when the TM is at this barrier position, there is already a first contact with the receptor surface (this causes the Landau energy to go down). This means that with increasing length of the TM moiety the barrier can be increasingly displaced from the receptor surface.

Systems for which $N_B < 30$ are most relevant as for these the TM remains inside the corona of the micelle when the receptor is far away. Now the minority chain is in a more or less homogeneously stretched conformation inside the corona region and the crown is missing. The main difference for shorter $N_B$ is that inside the corona, chains experience a repulsive brush potential that pushes the chain ends outward. This favors the bridging state. As a consequence, the binodal moves out to larger $\Delta r$ values, as can clearly be seen in Fig. 6a. The binodal has a shoulder at small $N_B$. Since $\Delta r$ is now larger, bridging chains must stretch more. This is probably why the energy barrier increases.

The height of the energy barrier at the binodal (cf. Fig. 6 (b)) is very low for small $N_B$. These low values indicate the capture efficiency of the TM for the receptor which is very high already at the binodal. Upon close inspection a rather complex behaviour manifests for $N_B < 40$. Apparently, flower-like conformations ($N_B > 30$) have a relatively low value for the barrier height at the binodal. Chains that must capture the receptor from inside the corona ($N_B < 30$) has a relatively high energy barrier: these chains first have to stretch to get out of the corona and then have to stretch further to go to the receptor (adding up to a relatively high $U^*$). Apparently as a result, near $N_B = 30$, we find $U^*$ to drop, but it must be kept in mind that the absolute value of the drop is small (just 0.1 $k_B T$). Indeed, we can see this non-monotonous behaviour of $U^*(N_B)$ because the absolute values of the barrier heights is small in this case. Below we find situations that the barrier height is significantly larger and then the irregularities for $U^*(N_B)$ near the value of the length of the minority chain for which flower-like conformations are found, are less visible.
1. Influence of the solvent quality $\chi_{\text{TM-H}_2\text{O}}$

Obviously, we can construct many different state diagrams and next, in Fig. 7, we will collect four different ones in a so-called collection of state diagrams. The different colours represent different values for the solvent quality of the TM: $\chi_{\text{TM-H}_2\text{O}} = 0.1, 0.4, 1.0$ and $3.0$. Meanwhile the values of the other parameters in the computations were maintained at: $\chi_{\text{TM-R}} = -3$, $\chi_{\text{TM-LGA}} = 1.0$, $N_{\text{TM}} = 3$ (as in the default state diagram Fig. 6). With decreasing solvent quality, i.e. increasing $\chi_{\text{TM-H}_2\text{O}}$ the binodal shifts to higher $\Delta r$ values, while the spinodal shifts to lower ones (Fig. 7 (a)). Meanwhile the height of the energy barrier at the binodal (Fig. 7 (b)) increases with decreasing solvent quality. Still the barrier height remains below the $3k_BT$ value so that the kinetics for the TM-R formation is still expected to remain sufficiently fast. The shift of the binodal with decreasing solvent quality is attributed to the fact that the TM-R affinity also has a solvent quality induced part; the effective adsorption energy increases slightly. Below we will see that with increasing affinity between the TM and the receptor the binodal shifts dramatically to the right.

One clear consequence of the increasing repulsion between TM and water is an induced adsorption energy for the TM to the core. This is reflected in progressively longer minority chains that can maintain their TM within the hydrodynamic diameter (in the absence of a receptor), reflected in the length of the solid curves in Fig. 7 (b). In more detail, when the TM has an affinity for the hydrophobic core, the minority chain has a loop-like conformation, similarly as the corona forming chains. For very poor solvent conditions, $\chi_{\text{TM-H}_2\text{O}} = 3.0$, the local minimum of the Landau energy near the surface appears and this implies a finite energy barrier near the core (i.e., a barrier associated to the desorption transition) and therefore the spinodal curve suddenly drops to very negative $\Delta r$-values, see Fig. 7 (a). Fortunately, as the energy barriers still remain modest, the spinodal curves are not very relevant in this case; the key feature is the binodal.

The intricate behaviour found for the $U^*(N_B)$-curves in Fig. 7 (b) easily catches our attention. However, the energies involved in these irregularities are very small. On top of the effect discussed above (the flower-like conformations having a lower barrier than internalized minority chains), we now also have an extra contribution to the desorption-transition of the TM from the core. Hence the extra energy needed to decouple the TM from the hydrophobic core and the stretching (unfolding) of the hydrophilic part of the diblock copolymer, may induce one extra maximum and/or minimum in $U^*(N_B)$, noticed for small values of $N_B$.

2. Influence of $N_{\text{TM}}$

In this subsection the attention is drawn to the number of segments at the end of the minority chain. Changes in this value represent a larger/smaller targeting moiety. Alternatively, $N_{\text{TM}}$ can be seen as a series of targeting moieties in a row. As an example, $N_{\text{TM}}=10$ and $\chi_{\text{TM-R}} = -3$ can be regarded either as a single targeting moiety of $\sim 1$ kDa with a total $\chi_{\text{TM-R}} = -30 (10 \times -3)$ or as 10 repetitive targeting moieties each with a $\chi_{\text{TM-R}} = -3$, the latter interpretation has our preference. The effect of the molar mass or repetition of targeting moiety ($N_{\text{TM}}$) units is collected in a collection
of state diagrams given in Fig. 8, lengths ranging from 1 to 10. Other parameters were the same as in the default state diagram Fig. 6.

Inspection of Fig. 8 (a) and (b) reveals a clear trend that more repeating targeting moieties gives a shift of the binodal and spinodal curves to larger \( \Delta r \) values and an increase of the corresponding energy barrier at the binodal; again all energy barriers \( U^* \) remain below \( 3 k_B T \). These trends may be explained by the fact that more repeating units of the targeting moiety effectively give a stronger TM-R interaction (see also results below). There may also be an entropic effect that as one particular TM-R contact is not realized there is in close vicinity another targeting moiety capable to connect to the receptor. There is a subtle effect that the larger \( N_{TM} \) requires a shorter \( N_B \) block length to keep the TM within the hydrodynamic diameter, see Fig. 8 (b). This implies that larger \( N_{TM} \) for the same \( N_B \) block lengths establishes TM-R contact at higher \( \Delta r \) values. When we add the length of the TM and the spacer \( N_B \) we again see that the non-monotonous behaviour of \( U^*(N_B) \) occurs at \( N_B + N_{TM} \approx 30 \), and thus should be attributed to the (undesired) formation of flower-like conformations of the minority chain (in the absence of the receptor).

3. The influence of the affinity of the TM for the receptor \( \chi_{TM-R} \)

In this section we take a closer look to the TM-R affinity parameter. A collection of state diagrams is presented in Fig. 9 for \( \chi_{TM-R} \) \(-3, -6, -12\) and \(-18\) while the remaining parameters were the same as the default state diagram in Fig. 6. In line with expectations we observe that the binodal distance shifts strongly, and in a linear fashion, to larger distances with increasingly negative values of \( \chi_{TM-R} \). Remarkable, as can been seen in Fig. 9 (a), for this range of parameters the spinodals overlap within the accuracy of the lattice model and hence there is just one dashed red curve. The corresponding values of the energy barrier at the binodal Fig. 9 (b) is a linearly increasing function of the absolute value of \( \chi_{TM-R} \). As the barrier can easily become larger than the threshold value of 3 \( k_B T \) (for the \( \chi_{TM-R} \) \(-3\) and \(-6\) values) we now also present for these cases the \( U = 3 \)-curve in Fig. 9 (a) (dotted curves). Again, these ‘practical spinodal’ curves are given because we envision that an energy barrier of \( 3 k_B T \) can easily be passed and these practical spinodal values are more relevant than the true spinodal (and the binodal) curves. The practical spinodal distances increase slightly with stronger affinities between TM-R. In passing we note that with increasing affinity of the TM for the receptor the irregularities in \( U^*(N_B) \) still exist but become less clearly visible.

As long as \( U^* < 3 \) we take the binodal and above this value the \( U = 3 \)-curve to estimate the relevant ‘capture distance’. Inspection of Fig. 9 (a) then reveals that with increasing affinity of the TM for the receptor the ‘capture distance’ increases continuously, but does not easily go beyond 10 nm (for \( N_B < 30 \)) value.

B. Optimization and discussion

Finally, after the assessment of the relevant modeling input parameters on the state diagram and the free energy barrier \( U^* \) we now zoom in onto systems with some preferred targeting design. The optimal design obeys to a set of conditions most of which we already encountered above. (i) The TM should not have a strong affinity for the core. As long as the affinity for the receptor exceeds that for the core, i.e. \( \chi_{TM-R} < \chi_{TM-LGA} \), the
translocation transition is still expected to occur. But, as soon as the affinity for the core is significant, the total free energy barrier, that is the desorption- plus translocation barrier, is expected to be correspondingly higher, so that the kinetics becomes progressively (exponentially) slower. (ii) There exists a minimum affinity of TM for R, $\chi_{TM-R} < -3$. When the affinity is too low the binding is not expected to take place in a significant fashion. (iii) The TM should not be too hydrophobic, that is, $\chi_{TM-H_{2}O} \lesssim 1$. Various complications are foreseen for hydrophobic TM. First of all, in the preparation the TM may be internalized inside the (glassy) core, and can then only be released when the core is degraded. Secondly, there is a solvent-induced affinity for the TM to adsorb onto the core. Then some extra energy is required to desorb the TM from the core. Thirdly, hydrophobic TMs are expected to have non-specific affinities for apolar substrates (molecules, receptors, tissues, membranes). Binding to these entities will decrease the ultimate efficiency of the targeting micelle. (iv) The minority chain should be short enough so that the TM is kept inside the corona as long as the receptor surface is not in capturing distance. When the minority chain is too short, the translocation is impossible. Hence the longer the minority chain the better. As long as the TM is ideally repelled by the core, the maximum length of the minority chain is $N_{TM} + N_{B} \sim 30$. (v) The number of repeating TMs along the minority chain is preferably not very small. In the current system we have focused on linear chain architectures. We argue that it stands also model for the case that a minority chain has a branched or dendritic end fragment which features several TM to be coupled to one or more receptors, albeit that the details for this will be slightly different. Alternatively, one can include multiple minority chains inside a micelle to enhance the capturing efficiency.

We argue that the capture distance, which is $\Delta r^{*}$ when the energy barrier is low, and the distance $\Delta r$ when $U = 3 k_{B}T$, should be as large as possible. When this value is sufficiently large the minority chain can in practical situations circumvent obstacles and wonder around, which is important when the micelle is near the individual receptors (different from our modeling assumption that the receptor is around the micelle). The following results are presented with the idea in mind to maximize the capture distance.

From these requirements we have identified two parameters which deserve a closer investigation, namely the affinity of the TM with respect to the receptor $\chi_{TM-R}$ (we choose values $-3, -6, -12$ and $-18$) and the number of repeating units of TM in the minority chain. Larger values of these two parameters give larger capture distances. Other parameters are the same as for the default system (cf. Fig. 6). This means that we still ignore a significant affinity of the TM for the core and insist on good solvent conditions for the TM ($\chi_{TM-H_{2}O} = 0.4$). The requirement to focus on the longest possible minority chain prompts us to fix the total length of the minority chain to $N_{TM} + N_{B} = 35$ (slightly larger than the value advised above to press our luck). In Fig. 10 we present a set of state diagrams in the coordinates $N_{TM}$ (longer values imply shorter spacer lengths $N_{B}$) versus the receptor distance $\Delta r$. As typically $U^{*} > 3$, we only present the spinodal curves (dashed) and the $U = 3 k_{B}T$ curves (dotted).

It follows that for $N_{B} + N_{TM} = 35$ a wide array of spinodals and practical spinodals $U = 3 k_{B}T$ can be realized. Let us first discuss the practical spinodals because these are of primary interest for the application. The practical spinodals (dotted curves) for $N_{TM} = 1$ (and $N_{B} = 34$) can be realized at $\Delta r = 2$ nm for $\chi_{TM-R} = -3$, $\Delta r = 4$
nm for $\chi_{TM-R} = -6$ and Δr = 6 nm for $\chi_{TM-R} = -12$ and -18 (the difference vanishes in the lattice approximations). The larger the $N_{TM}$ value the larger Δr for the practical spinodals, although for the smaller $\chi_{TM-R}$ values (−3 and −6) the practical spinodals reach a plateau value at Δr ≈ 5 nm for $\chi_{TM-R} = -3$ and at Δr ≈ 10 nm for $\chi_{TM-R} = -6$. Meanwhile the practical spinodals for $\chi_{TM-R} = -12$ and −18 still show a more or less linear growth of Δr with $N_{TM}$, enabling a record TM−R capturing distance Δr ≈ 6 nm up to Δr ≈ 15 nm for $N_{TM} = 20$. For the higher TM−R affinities the saturation of the ‘capture distance’ is expected to occur for even larger values of $N_{TM}$. Note that the practical spinodals for $\chi_{TM-R} = -12$ and −18 (dotted blue and green curves) are close to each other. For small values of $N_{TM}$ the practical spinodals for $\chi_{TM-R} = -12$ and −18 effectively coincide, while for larger values of $N_{TM}$ a constant difference of just ≈ 1 nm for Δr is maintained. This implies that the ‘capture distance’ is not easily increased by increasing the affinity $\chi_{TM-R}$ to even larger values. However, increasing $N_{TM}$ remains effective as a means to increase the capture distance as mentioned already. We will elaborate on why this is the case below.

The difference between the thermodynamic spinodal (dashed curves) and the practical spinodals (dotted curve) is indicative for the height of the energy barrier at the binodal, i.e. $U^*$. When this difference is very small the value of $U^*$ must be a bit larger than 3 $k_B T$, whereas when the difference is large, the barrier at the binodal is much larger than 3 $k_B T$, see also Figs 6 (a) and (b). With this information it is of interest to inspect the whereabouts of the spinodals. The spinodals (dashed curves) coincide at Δr∗∗ = 0 nm for $N_{TM} = 2$ (and $N_B = 33$) for all $\chi_{TM-R}$ values. Within the accuracy of the lattice, the spinodal for $\chi_{TM-R} = -6$, -12 and −18 overlap until $N_{TM} = 3$ from this value the spinodal for $\chi_{TM-R} = -6$ splits off, while the spinodals for $\chi_{TM-R} = -12$ and −18 still overlap until $N_{TM} = 5$. The spinodals (dashed curves) in comparison to the practical spinodals (dotted curves) first seem to go in parallel where-after they achieve a maximum difference and from thereon they converge back to each other. Again, the latter implies that $U^*$ increases with increasing $N_{TM}$. For the spinodals and practical spinodals of $\chi_{TM-R} = -3$ and −6 this behaviour can be completely monitored in Fig. 10. For the spinodal and practical spinodal of $\chi_{TM-R} = -12$ this behaviour can be seen until the maximum difference between the two spinodals (see blue curves). The spinodal and practical spinodal for $\chi_{TM-R} = -18$ (see green curves) only show the parallel part, and the other features are found for $N_{TM} > 20$ (not shown).

From this optimisation study we conclude that it is possible to increase the capture distance to at least 15 nm. This distance is significant as it is of the same order or a bit larger than the size of the corona. Apparently it is possible to stretch the minority chain by a factor of more than two to reach the receptor surface. Of course the relatively long series of TM contributes to this remarkable finding. A long sequence of TMs at the end of a relatively short spacer, allows the position of the barrier to be significantly displaced from the receptor surface. In a good approximation this distance scales linearly with $N_{TM}$ (not shown). The further the barrier is displaced from the receptor the less the minority chain has to stretch to reach the barrier. That is why the overall barrier height can remain so low while the receptor is relatively far away.

Thus far we only focused on a single minority diblock copolymer per micelle. We note that while using the nanoprecipitation method the diblock copolymers are distributed randomly over the micelles and hence it is impossible to achieve exactly one diblock copolymer per micelle. This implies that some micelles certainly will contain more diblock copolymers, while others remain empty. In order to prevent that some micelles contain no diblock copolymers it is advised to aim at an average of e.g. $\approx 10$ diblocks per micelle in order to achieve that at least the majority of all micelles contain at least one diblock per micelle. Also in order to increase the probability on TM−R contact we should incorporate more than one diblock copolymer per micelle. We recall that the corona is composed of over 200 tri-block copolymers and therefore having 10 minority chains is still expected to be only a slight perturbation. We have checked that this is indeed the case (not shown). In these cases we found that each minority chain behaves independently from all the others and therefore we simply can linearly add up the capture efficiency. In other words, the probability for
a TM-R contact will increase linearly with the number of minority chains per micelle.

Here we only focused on repeating TM in a linear chain-architecture. Other architecture can still be handled by the SF-SCF machinery. It can be that other geometries (star-like or dendrimer-like) have even a more pronounced effect on TM-R contact and \( \Delta r \). These could even be used with larger values for \( N_B \) while maintaining the TM within the hydrodynamic diameter and enabling TM-R contact at larger \( \Delta r \). To study such modifications becomes appropriate when corresponding experimental systems become available.

There are several ways to check the viability of our SF-SCF modeling approach and we hope such experiments will be performed in the near future. One can, for instance, investigate the strength or possibility of a TM-R connection with atomic force microscopy to generate or validate the parameters needed. Another way of checking the efficiency of the hidden targeting moieties within the micellar corona and their receptor interaction is by exposing the micelles to specific antibodies for their targeting moieties. Comparing against micelles which do not contain targeting moieties with micelles that contain their targeting moieties beyond (flower-like conformations) and within the micellar corona (homogeneously stretched conformations). A similar experiment can also be performed with an immune response evoking targeting moiety. Again, when the TM is hidden inside the corona this should avoid an immune response, while a clear immune response is generated when the (too long) minority chains are in the flower-like conformation which exposes the TM.

IV. CONCLUSIONS

Copolymer micelles are promising structures for passive and active drug delivery applications. Experimentally it is attractive to use the nanoprecipitation method to generate micelles with a well-defined structure and composition. This method can be adopted to include targeting moieties without the need to perform elaborate post-processing of the micelles. In this paper a modeling approach has been presented aimed at finding the best parameters for such composite micelles to perform as active delivery vehicles. We hope that this modeling study allows for a more efficient design of active drug delivery micelles in medical applications.

We have used the Scheutjens-Fleer Self-Consistent Field (SF-SCF) theory in a spherical coordinate system with concentration gradients in one direction, and implemented a coarse grained model with appropriate parameters that closely predict the micellar structure when triblock copolymers with the PLGA-PEO-PLGA architecture self-assemble through the solvent-precipitation method. We postulated that it is possible to admix a small number of diblocks PLGA-PEO into these micelles without affecting the overall micelle structure. We reported an SF-SCF analysis to reveal which diblock copolymer molar masses/block lengths are beyond or hidden within the corona the micelles. We then focused on the hidden ones: these systems avoid the possible immune response upon their application in the human body. At the free end of the diblock copolymer a targeting moiety (TM) or a series of TMs are attached and we have positioned a receptor surface around a (slightly simplified) composite micelle in a cell-model. A parameter search was executed to find the largest possible capture distance, that is, the distance between the receptor and the micelle at which the TM-R contact is efficiently established. We have introduced a Landau free energy as a function of the distance of the receptor (surface) to the micelle and identified the so-called translocation transition, wherein the TM jump-like goes from the hidden position inside the corona to the receptor which is outside the corona. Here the ad-hoc estimate was taken that the free energy barrier (the minority chain has to stretch to reach the receptor) for the translocation transition should be about \( 3 k_B T \) to estimate the experimentally relevant capture distance. We have shown that it is possible to reach capture distances of at least 15 nm. This length corresponds to the size of the corona and implies that it should be possible to double the stretching of the minority chain in the process of capturing the receptor. On top of this a number of design rules were formulated. For example, we advised that the TM should not be too hydrophobic. It is also better to prevent specific adsorption of the TM onto the core of the micelle. It is expected that the number of minority chains in the micelle can be larger than unity without adverse effects. More chains imply a higher capture efficiency, but increasing the value too much will perturb the micelle structure in unforeseen ways. We also speculated that a branching of the terminal end of the minority chain can be used to further improve the design.

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