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Forces on an attractive surface generated from a thermoresponsive polymer gel

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Interaction between polymers and soft-matter surfaces in the biological cell is a common yet incompletely understood phenomenon. This work investigates a generic situation where a thermoresponsive polymer gel is placed in the vicinity of an adsorbing surface, and starts contracting. The force is mediated by polymer chains that partially attach to the surface and partially to the contracting gel. The main goal was to understand how the force generated by the transforming polymer gel depends on key parameters that describe the system, most importantly, the concentration of the polymer, the length of the force-mediating polymer, and the the distance between the surface and the outer border of the contracting polymer gel. The key result of the paper is the Laplace transform (with regard to the polymer length) of the pulling force expression. Analytical approximations for the force have been obtained, and the exact expression for the pulling force is presented for the situation when the gel starts contracting. In depth analysis of the force behavior revealed several phases adopted by the polymer during the gel contraction. © *2014 Author(s). All article content, except where otherwise noted, is licensed under a Creative Commons Attribution 3.0 Unported License.* [http://dx.doi.org/10.1063/1.4894269]

I. INTRODUCTION

A. Background

There are many instances in cell biology where polymers interact with soft-matter surfaces. We had previously obtained direct experimental evidence for polymer-induced nanotube pulling from a self-assembled phospholipid membrane (Figure 1), that strongly suggests that the pulling action of polymer chains produces a significant force. In fact, this force could could be an important factor in biomembrane transformations, such as deformation and tubulation. It has been shown that lipid nanotube formation is common in cellular organelles, in particular in the endoplasmic reticulum (ER) and the Golgi apparatus, between organelles or in the form of filopodia, responsible for, *e.g.*, cell motility.[1–5] Although protein action on the cell membrane in combination with actin polymerization has been suggested as a mechanism driving lipid nanotube or exocytotic transport carrier formation,[6] polymer-membrane interactions might also be involved in nanotube formation by means of pulling action.[7]

Apart from the in vivo examples discussed above, several engineering applications have been reported where polymer-decorated surfaces were used to control cell adhesion and release. For example, thermoresponsive surfaces enabled cell sheet engineering in the context of cell culturing and clinical applications.[8]

The formation of tubes is one of the many possible outcomes of polymer-membrane interactions in the biological context. It seems prudent to investigate what the force on the surface, generated

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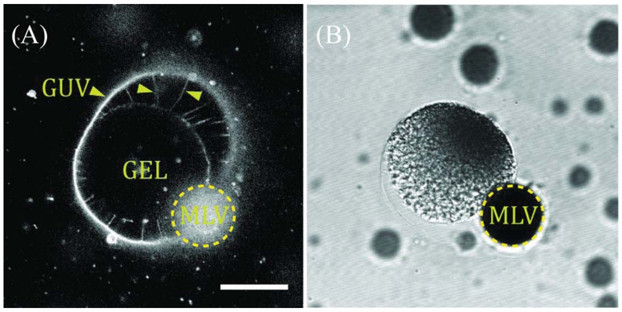

FIG. 1. Polymer-biomembrane interactions in a giant unilamellar vesicle. (A) Confocal image of the system. A contracted PNIPAAm-VFc hydrogel deforms the spherical liposome and pulls nanotubes from the membrane towards the gel compartment. The vesicle membrane along with the nanotubes are visualized with the membrane stain FM1-43. (B) Bright field differential interference contrast micrograph of the same polymer during gel compartment formation inside the vesicle. The nanotubes are not visible. The unilamellar vesicle is connected to a multilamellar vesicle, which acts as membrane source for inflation of the unilamellar liposome. Scale bar: $30 \mu m$. Arrows point towards the vesicle membrane and highlight some of the formed nanotubes.

by a dense polymer gel, depends on. In particular, can an analytical expression for this force be obtained?

Here we present a theoretical study of the forces that polymers can generate when they interact with a membrane surface. We specifically investigate how the dynamics of polymer chains influences the force on a generic adsorbing membrane.

B. The model

In the earlier pulling experiments (Fig. 1) a hydrogel was generated inside a lipid membrane shell (vesicle). By manipulating the temperature of the system slightly, the gel was forced to contract, and polymer chains, which are in contact with both the gel and the membrane (force mediator polymers), deformed the membrane, which could be easily visualized. This provides us now with an experimental setup on which to test some of our theoretical findings qualitatively.

Note that with respect to these experiments we refer in the following to the interacting soft-matter surface as “membrane”, although we never model biological membrane mechanics. The focus of our study is on understanding how the force is generated by the dynamics of the polymers that mediate the contact between the gel and the membrane surface.

Figure 2 shows essential geometric features of the theoretical model we constructed accordingly. There are three parameters that define the geometry of the system, the vesicle radius R, the radius of the gel g, and the distance from the vesicle membrane to the surface of the gel $w = R - g$. To be able to build an analytically solvable model a spherical symmetric setup is employed and several simplifying assumptions have been made. For example, the membrane mechanics and dynamics are neglected (polymer relaxation times are much faster than the membrane shape changes).

The pulling action of the gel on the polymer is modelled by assuming an attractive potential between the polymer and the gel, and likewise for the interaction between the polymer and the membrane. The dynamics of mediator polymers is described by using the Gaussian chain model in which polymer configurations correspond to random walks in three dimensional space with an external potential.

The parameters that define the model are the concentration of the polymer in the gel C_0, the excluded volume parameter v, the polymer length n, the Kuhn length a, the distance of the outer gel surface from the membrane w (as illustrated in the figure), the polymer-membrane interaction strength c, and the temperature of the system T. The concentration of polymers in the gel is assumed to be constant. The excluded volume parameter v describes how polymer chains interact with each other. Negative values imply attraction, and positive values repulsion. The polymer-membrane interaction strength is described by using the de Gennes theory of polymer adsorption, where c^{-1} is the effective adsorption length parameter.

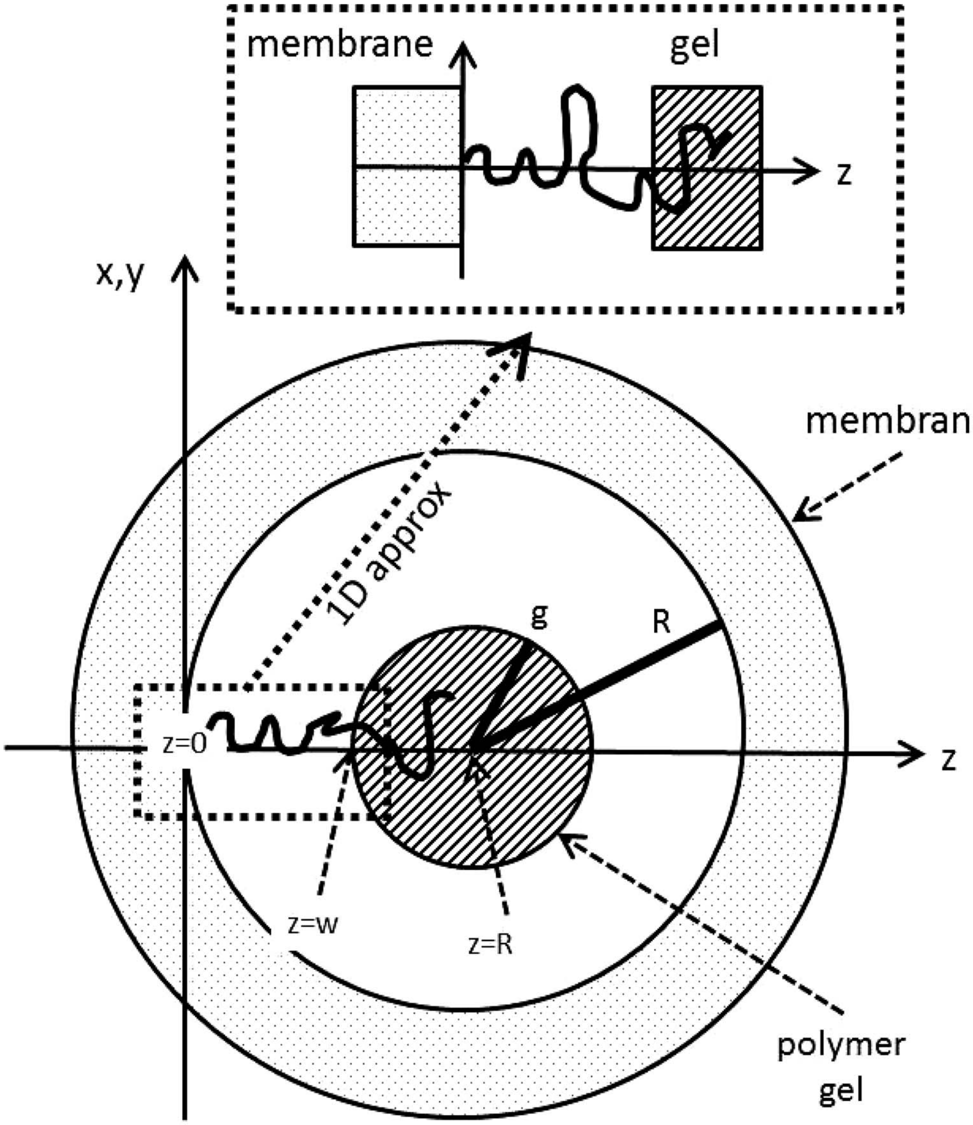

FIG. 2. The theoretical setup. A perfect spherical symmetry is assumed. The radius of the membrane is R, and the radius of the polymer gel is g. The distance from the membrane surface to the gel surface is $w = R - g$. The polymer is anchored with one end at the membrane. The origin of the local Cartesian system is placed at the contact point. The inset shows that for the region close to the membrane the system appears as one-dimensional.

The goal is to understand how the force that the polymer exerts on the membrane depends on the parameters v, c, C_0, n, a, w, and T that define the system. We have found a way to solve the problem analytically and obtained a qualitative understanding of how the pulling force depends on the parameters that define the system.

To the best of our knowledge there are very few theoretical models of polymer membrane interactions. There are some studies that focus on investigating how a polymer interacts with the infinite flat and rigid membrane of finite width.[9–11] There are also related studies of how polymers embedded in a closed volume exert a force on rigid boundaries, many of them focused on studying polymers near or in-between infinite planes.[12–18] Very few studies specifically investigate how polymers interact with flexible boundaries that can bend under the influence of the polymer.[19–21] An interesting work has been published[22] which showed that hydrophobic polymer-solvent interactions can induce effective attraction between the membrane and the polymer. This study motivated our

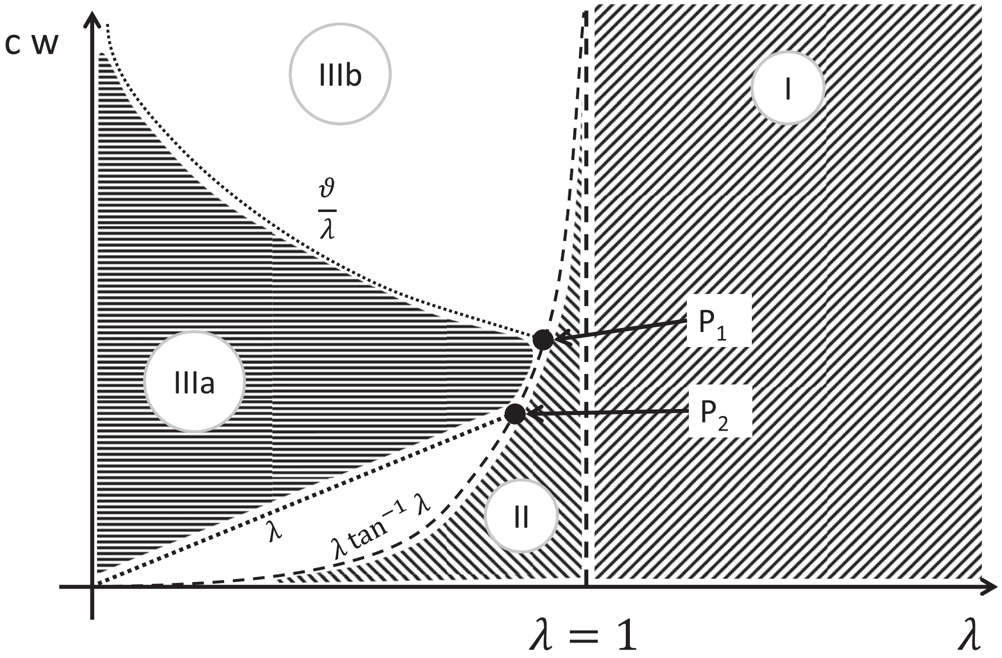

FIG. 3. The phases of the system. I: A very robust adsorbed phase. II: Adsorbed phase. IIIa: Desorbed (force plateau) phase. IIIb: Adsorbed phase.

decision to focus on attractive polymer-membrane interactions. We assume that a similar situation occurs when the gel starts contracting.

C. The most important results

Before discussing the technical steps necessary for solving the model, a brief summary of the key results will be given. Our model predicts several characteristic force behaviors which correspond to various phases that the polymer adopts during its action. Figure 3 shows the phase diagram of the system. The behavior of the system is controlled by two dimensionless parameters, the product cw, and the parameter $\lambda = c/\sqrt{u}$ where $u = |v|C_0$. The parameter u describes the polymer-gel interaction potential. The combination cw measures the distance of the gel from the membrane in units of the adsorption length. The parameter λ measures the polymer-membrane adsorption strength relative to the strength of the polymer-gel interaction potential u. We currently do not have an explanation why the square root of u is involved in the combination.

The phase diagram contains the following states. The polymer can be adsorbed, and there are two adsorbed states I, II/IIIb. We believe that II and IIIb are the same. In state I the polymer is adsorbed strongly. This phase is very robust. For all distances w the polymer stays adsorbed regardless of how strongly the gel pulls the polymer. In state II/IIIb the adsorption is weaker. In this phase the polymer can be peeled off the membrane depending on the outcome of various mechanisms (entropic cost of straightening the polymer, versus energetic cost gained by interaction with the gel). The distance w also plays a role. If the gel is too close to the membrane, the polymer stays attached but we expect that the polymer is not strongly attached as in phase I. IIIa denotes a desorbed phase, when the polymer is peeled off (detached) from the membrane. This happens when the distance w is large enough, but not too large, since the polymer is adsorbed again when the gel moves far away from the membrane. Each polymer state leads to a different mode of force transmission.

Another interesting feature of the model is that it suggests that there is a possibility that the force even increases with w (e.g. Fig. 4). This can happen since the polymer concentration increases as the gel contracts. The gel contraction makes the parameter u larger with increasing w. Thus there are two effects that work against each other, the natural decay of the force due to the fact that gel

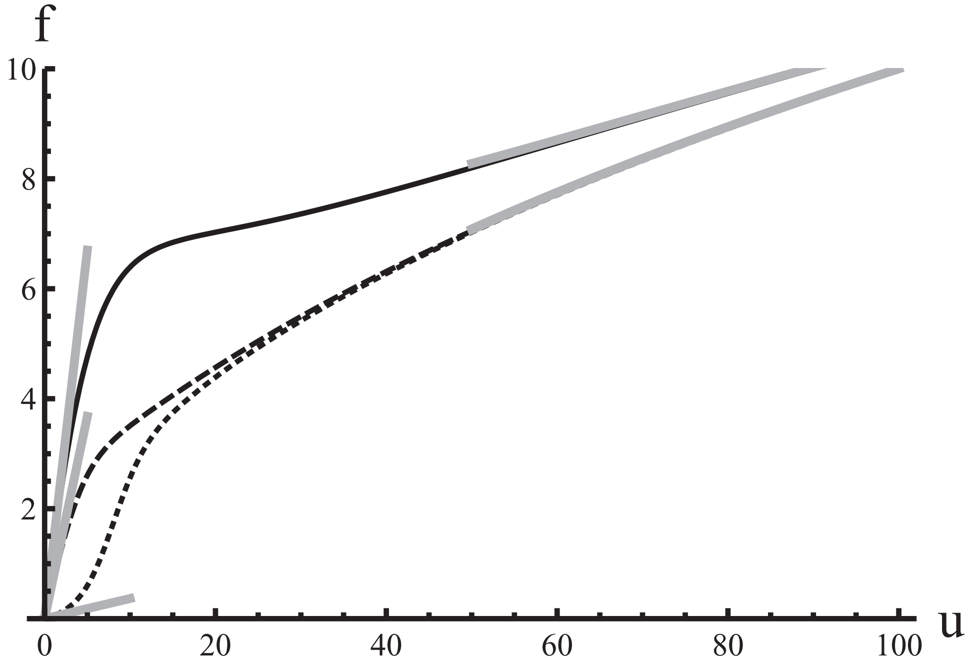

FIG. 4. The pulling force increases with u. The force is plotted as a function of u for the following values of w: $w = 0.2$ (the full line), $w = 0.5$ (the dashed line), and $w = 2$ (the dotted line) with $c = 1$. The gray lines near the origin depict the respective small u approximations. The same line types for large u values were plotted using the respective large-u approximations.

looses a hold on the polymer, and the increase in the force due to the gel contraction. There is a subtle balance between the two that determines the outcome. We showed that the force indeed can increase with distance due the change in the polymer concentration. This behavior occurs when the condition $R \lesssim c^{-1}$ is met, i.e. for vesicles that are not too large.

In general, we observed exponential-like decay of the force as the polymer-gel distance is increased. This happens when the polymer stays adsorbed on the membrane during the interaction process. However, there is a possibility that the force does not decrease with the distance but stays constant. This behavior is illustrated by existence of the plateau regions featured in the plots that depict how the force depends on distance (e.g. Fig. 5). The occurrence of the force plateau was rather unexpected. This behavior occurs when the polymer is in the desorbed phase.

Finally, we managed to obtain an analytic expression for the pulling force exactly at the point when the gel starts contracting (at $w = 0$). To obtain this result a highly non-standard evaluation is involved, which will be discussed in great detail. The force expression agrees qualitatively with experimental results. There is a critical concentration value that governs whether the pulling is possible or not. This critical concentration decreases with increasing polymer length. Furthermore, we showed that the force expression at $w = 0$ is very useful from a practical point of view. Our analysis revealed that this force defines the order of magnitude for the force at all distances.

Thus, we present a minimal model and provide a (semi) analytical solution. Detailed explanations are presented in the following sections. Section II contains a brief explanation of how the force can be estimated if the free energy of the polymer is known. In Section III general guidelines for computing the free energy are given. It is shown how the problem can be approximated as an one-dimensional problem. The solution of the one-dimensional problem is demonstrated in Section IV. Section V contains details of the derivation. A phase diagram that summarizes the behaviour of the model is presented in Section VI, followed by some numerical results in Section VII. Finally, in Section VIII a qualitative comparison with experimental results is presented. Appendices contain details on the experimental procedures.

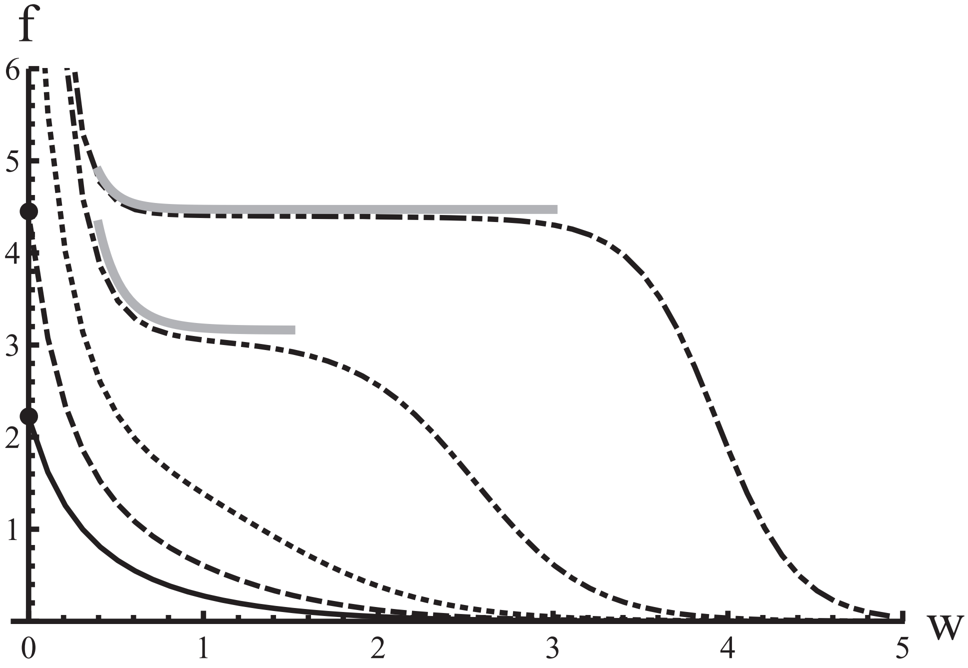

FIG. 5. The pulling force decreases with w. The force is plotted as a function of w for the following values of u: $u = 1$ (the full line), $u = 2$ (the dashed line), and $u = 4$ (the dotted line), $u = 10$ (dash-dot), and $u = 20$ (dot-dot-dash), all with $c = 1$. The black circles indicate the values obtained by the exact force formula at $w = 0$. For large values of u there is a plateau predicted by the analytic analysis in the text. The gray lines were obtained by plotting respective analytic approximation for the pulling force.

II. FORCE COMPUTATION ESSENTIALS

In such a setup the force on the membrane can be estimated by using the standard thermodynamic arguments which give

$$f_M(w) = -\frac{\partial}{\partial w} F(w, \vec{r}_0 \in M) \tag{1}$$

where $F(w, \vec{r}_0)$ is the free energy of the system for a fixed w when one polymer end is placed at $\vec{r}_0$, and M denotes the membrane surface. This expression can be obtained from the following phenomenological reasoning.

The pressure of the system (the polymer, the solution inside, and the gel) on its surroundings (the membrane) is given by

$$\frac{f_M}{A} = -\left[\frac{\partial F}{\partial V}\right]_T \tag{2}$$

where A is the area of the membrane. The formula simply states that under the constant temperature the work done by the system can only come at the expense of the free energy.

The membrane plays the role of a containing surface. The internal energy of the system is composed of the contributions coming from (a) the polymer-membrane interaction, (b) the polymer-gel interaction, and (c) the polymer-solvent interaction. The force formula (2) follows by assuming a spherical membrane shape, and the fact that $dV = AdR = Adw$ (the radius of the gel g is assumed constant when the differentials are computed). The force formula is rather phenomenological and likely overestimates the force. However, it is technically feasible and very intuitive.

By convention the positive force points always towards the outside of the containing volume. In the following, a convenient sign convention will be introduced for the force to simplify the notation.

The pulling force f is defined as the negative of the force on the membrane

$$f \equiv -f_M \tag{3}$$

In such a way the positive sign of f indicates that the membrane is being pulled inwards.

III. THE FREE ENERGY COMPUTATION

The free energy of a mediator polymer can be computed by using the standard techniques.[23] The free energy can be expressed as

$$F(w, \vec{r}_0) = -k_B T \ln \mathcal{Z}(w, \vec{r}_0) \tag{4}$$

where k_B is the Boltzmann constant, T denotes the temperature, and $\mathcal{Z}(w, \vec{r}_0)$ is the partition function given by

$$\mathcal{Z}(w, \vec{r}_0) = \gamma^n \int d^3\vec{r} G(\vec{r}, n|\vec{r}_0, 0) \tag{5}$$

where n is the number of monomers in the chain, γ defines the number of the degrees of freedom per monomer, and G denotes the Green function of the polymer. The Green function specifies the statistical weight of all polymer conformations with one end fixed at $\vec{r}_0$ and the other one at $\vec{r}$. The integral is being taken since the second end at $\vec{r}$ is free to fluctuate. The first term, γ^n, is the partition function for the free polymer. The second term describes the corrections due to the presence of the membrane and the gel.

The Green function is computed by using the ideal chain approximation of Doi and Edwards

$$-\frac{\partial G}{\partial n} = \left[-\frac{a^2}{6} \nabla_r^2 + \beta U(\vec{r}) \right] G \tag{6}$$

where a denotes the Kuhn length of the polymer and $U(\vec{r})$ is the potential felt by each monomer, describing the interaction with the membrane and the gel. In the following sections we discuss how it can be solved approximatively.

A. One dimensional approximation

The first simplification made is that the radius of the vesicle R is very large in comparison to any length-scale in the system, and in particular $R \gg w$. Then, the region in between the gel and the membrane can be approximated as in the inset of Fig. 2. The problem becomes effectively one dimensional. The Green function factorizes as

$$G(\vec{r}, n|\vec{r}_0, 0) \approx G_0(x, n|x_0, 0) G_0(y, n|y_0, 0) G(z, n|z_0, 0) \tag{7}$$

where G_0 denotes the Green function of the free chain. The function $G(z, n|z_0, 0)$ has to be found by solving a one-dimensional Doi-Edwards equation. Once the Green function is known the pulling force on a broad membrane patch can be computed as

$$f = -k_B T \frac{\partial_w \varphi}{\varphi} \tag{8}$$

where

$$\varphi = \int_0^{z_{\max}} dz G(z, n|z_0 = 0, 0) \tag{9}$$

The upper integration limit clearly cannot exceed the vesicle radius R. For simplicity reasons we take $z_{\max} \sim R$. Later on it will be assumed that $R \to \infty$.

B. Polymer membrane interaction

A further simplification is to assume that the potential that describes the polymer membrane interaction allows for the approximation justified by de Gennes,[24]

$$\left[\frac{\partial_z G}{G} \right]_{z=0} = -c \tag{10}$$

where $c > 0$ ($c < 0$) indicates adsorption (repulsion) between the polymer and the membrane. We describe the possibly complex interaction potential between the membrane and the polymer by a relatively simple boundary condition.

C. Polymer-gel interaction

In the mean-field approximation[23] the polymer-gel interaction potential is given by

$$U(\vec{r}) \approx k_B T v C(\vec{r}) \tag{11}$$

where $C(\vec{r})$ is the concentration of the monomers in the gel and v is the excluded volume parameter. For hydrophobic chains this parameter is negative.

In the one-dimensional approximation the potential is given by

$$\beta U(z) = u\Theta(z \geq w) \tag{12}$$

where $\Theta(z \geq w)$ is zero unless $z \geq w$. The parameter u is given by

$$u = \frac{|v|C_0}{(1 - w/R)^3} \approx u_0(1 + 3\frac{w}{R}) \tag{13}$$

where $u_0 \equiv |v|C_0$ is a dimensionless parameter that describes how strongly the polymer and the gel interact when $w = 0$, *i.e.,* when the gel is initially formed. The term in the denominator comes from the fact that as the gel contracts its density increases. Assuming that the concentration of the monomers in the gel is uniform leads to the correction in the denominator. To stay consistent with the linear approximation, the expansion to the first order in w/R will be used.

IV. FORMAL SPECIFICATION AND THE SOLUTION OF THE ONE-DIMENSIONAL PROBLEM

For practical purposes it is convenient to re-scale all parameters and work with dimensionless quantities. The fundamental length in the system is the Kuhn length which defines the unit of length $\kappa \equiv \sqrt{a^2/6}$. All re-scaled distances are defined as $z \equiv \tilde{z}\kappa$, $z_0 \equiv \tilde{z}_0\kappa$, $w \equiv \tilde{w}\kappa$. The dimensionless Green function is defined as $G \equiv \tilde{G}/\kappa$ and likewise for the de Gennes c-parameter one has $c = \tilde{c}/\kappa$. The integral of the Green function does not have to be re-scaled since one can easily show that $\tilde{\varphi} \equiv \varphi$. The pulling force is transformed as $f = k_B T \tilde{f}/\kappa$. From now on, the *tilde* sign will be omitted on all symbols.

The assumptions at hand lead to the following form of the one-dimensional Edwards-Doi equation

$$\frac{\partial^2}{\partial z^2} G(s, z|z_0) - [s - u\Theta(z > w)]G(s, z|z_0) = -\delta(z - z_0) \tag{14}$$

where the Laplace transform of the Green function is defined as

$$G(s, z|z_0) \equiv \int_0^\infty dn\, e^{-sn} G(z, n|z_0, 0) \tag{15}$$

The boundary conditions are as follows. Equation (14) has to be solved with the following boundary condition at the membrane

$$[\partial_z G(s, z|z_0) + cG(s, z|z_0)]_{z=0} = 0 \tag{16}$$

To simplify the technical part of the problem it is assumed that the $R \to \infty$ limit can be taken. Thus, far away from the membrane one has

$$\lim_{z\to\infty} G(s, z|z_0) < \infty \tag{17}$$

Furthermore, the Green function has to be continuous at $z = z_0$ and exhibits a jump in the derivative:

$$G(s, z_0^+|z_0) = G(s, z_0^-|z_0) \tag{18}$$

$$\partial_z G(s, z_0^+|z_0) - \partial_z G(s, z_0^-|z_0) = -1 \tag{19}$$

where $z_0^\pm \equiv \lim_{\epsilon\to 0} z_0 \pm \epsilon$.

The Doi-Edwards equation can be solved analytically, and one obtains the following expression for the Laplace transform of the one-dimensional partition function $\varphi(n)$:

$$\varphi(s) = \frac{\Phi}{\sqrt{s}\sqrt{s-u}\,\Psi} \tag{20}$$

with

$$\Phi = u + (s-u)\cosh[w\sqrt{s}] + \sqrt{s}\sqrt{s-u}\,\sinh[w\sqrt{s}] \tag{21}$$

and

$$\begin{aligned} \Psi = {} & \sqrt{s}(\sqrt{s-u} - c)\cosh[w\sqrt{s}] + \\ & +(s - c\sqrt{s-u})\sinh[w\sqrt{s}] \end{aligned} \tag{22}$$

V. FINDING THE INVERSE LAPLACE TRANSFORM AND AN ANALYSIS OF THE SOLUTION

The expression for $\varphi(n)$ can be found by using the usual techniques for finding the inverse Laplace transform. We only indicate the results. One can easily show that $s = 0$ and $s = u$ are not poles, but branching points. If it exists, there is only one pole at $s = s_*$. The pole is given by the root of the equation

$$\Psi(s_*) = 0 \tag{23}$$

Unfortunately, the root can be specified only in this implicit form.

If it exists, the root is real and it lies in the interval $u \leq s_* \leq u + c^2$. The root exists if and only if the condition

$$\tanh[w\sqrt{u}] \leq \frac{c}{\sqrt{u}} \tag{24}$$

is satisfied. Note that the condition above holds for any w if $u < c^2$. This implies that if the potential well is not too deep there is always a pole.

The expression for $\varphi(n)$ contains three contributions coming from the two branch-cut integrals and a pole contribution:

$$\varphi(n) = \varphi_\Gamma(n) + \varphi_\gamma(n) + \varphi_*(n) \tag{25}$$

$$\varphi_\Gamma(n) = -\frac{1}{\pi}\int_0^\infty d\xi\, e^{-\xi n}\frac{1}{\sqrt{u+\xi}}\frac{c + cu\frac{1-\cos[w\sqrt{\xi}]}{\xi} - \frac{u}{\sqrt{\xi}}\sin[w\sqrt{\xi}]}{c^2 + \xi + u\left(\cos[w\sqrt{\xi}] - \frac{c}{\sqrt{\xi}}\sin[w\sqrt{\xi}]\right)^2} \tag{26}$$

$$\varphi_\gamma(n) = \frac{1}{\pi}\int_0^u d\eta e^{\eta n}\frac{1}{\sqrt{u-\eta}}\frac{-c + cu\frac{1-\cosh[w\sqrt{\eta}]}{\eta} + \frac{u}{\sqrt{\eta}}\sinh[w\sqrt{\eta}]}{c^2 - \eta + u\left(\cosh[w\sqrt{\eta}] - \frac{c}{\sqrt{\eta}}\sinh[w\sqrt{\eta}]\right)^2} \tag{27}$$

$$\varphi_*(n) = \Xi\, e^{s_* n} \tag{28}$$

If the pole does not exist $\varphi_*(n) \equiv 0$. Note that the second integral, φ_γ, can be rewritten in a form that resembles the first integral, φ_Γ, by introducing the substitution $\eta = -\xi$ and using the usual analytic continuation formulas for the trigonometric functions. The amplitude Ξ in the the pole contribution comes from computing the following residue

$$\Xi = \mathrm{Res}\left[\frac{\Phi}{\sqrt{s}\sqrt{s-u}\,\Psi}, s = s_*\right] \tag{29}$$

The residue is essentially given by the derive of Ψ. This derivative can be split in two parts as $\Psi' = \Psi'_1 + \Psi'_2$ that behave differently in the $w \to 0$ limit. The residue can be expressed as

$$\Xi = \left[\frac{\Phi}{\bar{\Psi}'_1 + \bar{\Psi}'_2} \right]_{s=s_*} \tag{30}$$

where the individual parts are given by

$$\bar{\Psi}'_1 \equiv \sqrt{s}\sqrt{s-u}\,\Psi'_1 \tag{31}$$

$$\bar{\Psi}'_2 \equiv \sqrt{s}\sqrt{s-u}\,\Psi'_2 \tag{32}$$

For each of the expressions there are two interchangeable versions:

$$\bar{\Psi}'_1 \overset{\text{v1}}{=} \frac{u\left(c\sqrt{s-u}+s-c^2\right)}{2s\sqrt{s-u}\left(c-\sqrt{s-u}\right)} \sinh[w\sqrt{s}] \tag{33}$$

$$\bar{\Psi}'_1 \overset{\text{v2}}{=} \frac{u\left(c\sqrt{s-u}+s-c^2\right)}{2\sqrt{s}\sqrt{s-u}\left(s-c\sqrt{s-u}\right)} \cosh[w\sqrt{s}] \tag{34}$$

$$\bar{\Psi}'_2 \overset{\text{v1}}{=} \frac{uw\left(s-c^2\right)}{2s\left(c-\sqrt{s-u}\right)} \sinh[w\sqrt{s}] \tag{35}$$

$$\bar{\Psi}'_2 \overset{\text{v2}}{=} \frac{uw\left(s-c^2\right)}{2\sqrt{s}\left(s-c\sqrt{s-u}\right)} \cosh[w\sqrt{s}] \tag{36}$$

A. A speculation on the existence of the pole: adsorbed and desorbed states

If the pole is present, and the polymer is very long, the partition function scales as $\mathcal{Z} \sim \gamma^n \exp[s_* n]$. This resembles the form of the partition function of a polymer in a globular state. This suggests that the presence (absence) of the pole s_* is an indication that the polymer is in an adsorbed (desorbed) state. However, one has to be careful with this interpretation.

For example, we noticed an interesting behavior of the φ_γ integral. If the pole is not present, the branch cut integral φ_γ can instead acquire a pole-like singularity when $w \to \infty$. In this limit, the branch-cut integrand behaves as the delta-function $\delta(\eta - c^2)$. Interestingly, at the value of w when the pole is lost, *e.g.* $w = w_*$, the integral becomes discontinuous, where w_* is defined by

$$\tanh[w_*\sqrt{u}] = \frac{c}{\sqrt{u}} \tag{37}$$

The sum $\varphi_\gamma + \varphi_*$ is continuous in w. As the other integral φ_Γ is always continuous in w, the φ is also continuous. This implies that the discontinuity is purely mathematical.

A rigorous analysis of the polymer states would involve studying how the Green function decays for large z. We did not investigate this further. The following formal definitions of states will suffice: A system is in an adsorbed (desorbed) state when the pole is (not) present.

B. Exact force at zero distance

We implemented Eqs. (25)–(28) numerically so that the partition function could be computed for any choice of Â´the parameters n, c, u, and w. In addition, the equations were investigated analytically for some special limits of these parameters. For example, we managed to find the exact expression for the pulling force when $w = 0$ (*i.e.* the gel just formes):

$$f_0 = \frac{u}{c}\left(2\vartheta + \frac{2}{\sqrt{\pi}} \frac{\sqrt{\vartheta}e^{-\vartheta}}{1+\text{erf}[\sqrt{\vartheta}]}\right) \tag{38}$$

with

$$\vartheta \equiv c^2 n \tag{39}$$

where $f_0 \approx 2cun$ and $f_0 \approx 2u\sqrt{n}/\sqrt{\pi}$ for long and short chains, respectively. It will be shown later that Eq. (38) can be used to obtain the order of the magnitude of the pulling force.

The force expression can be obtained as follows. Only the main steps of the force derivation will be discussed. Since the $w \to 0$ limit is implicit, the condition for pole existence is always satisfied, and the pole contribution has to be always considered. One can evaluate the derivative ∂_w of the branch cuts φ_Γ and φ_γ, and the pole contribution φ_* separately. It is possible to simplify the derivation somehow by evaluating the derivative over w by taking the derivative under the branch cut integral signs, evaluating the $w \to 0$ limit, and then integrating. The pole contribution can be treated in a similar way by applying ∂_w on the contour integral

$$\varphi_*(n, w) = \lim_{\epsilon \to 0} \left[\frac{1}{2\pi i} \oint ds e^{sn} \varphi(s, w) \right]_{s = s_*(w) + \epsilon e^{i\theta}} \tag{40}$$

where $\theta \in [0, 2\pi]$. Note that while evaluating the derivative under the integral sign, $\partial_w ds = 0$ and $\partial_w s = \partial_w s_*(w)$. The derivative of the pole position over w is given by $\lim_{w \to 0} \partial_w s_*(w) = -2cu$. This can be obtained by studying the pole equation (23). The derivative ∂_w can be taken under the integral signs due to the uniform convergence of the improper integrals and the continuity of $\varphi(s, w)$ for small w.

C. The Force in the limit of a weak potential

For weak polymer-gel interaction, *i.e.,* when $u \to 0$, it is possible to find an approximative solution to the root equation (23). In this limit

$$s_* \approx c^2 + u \frac{1 - \tanh[cw]}{1 + \tanh[cw]} + \mathcal{O}(u^2) \tag{41}$$

and the one dimensional partition function can be approximated by

$$\varphi(n) \approx 2e^{s_* n} \tag{42}$$

which results in the following force expression

$$f \approx 2ucne^{-2cw} \tag{43}$$

The force decays exponentially with w. This suggests that once the gel has moved outside the range of the adsorption length $1/c$, it cannot take hold of the polymer, and the force rapidly decreases to zero.

D. Long chain, or strong potential, approximation

It is possible to use the standard techniques to study the limit of very long chains. The analysis differs, depending on whether there is a pole or not.

The pole exists (adsorbed state): If the pole exists then the asymptotic behavior is governed by the pole contribution

$$\varphi(n) \sim \Xi e^{s_* n} \tag{44}$$

For very long chains the dominant contribution to the pulling force is given by

$$f \sim -n \partial_w s_*(w) \tag{45}$$

In this state, the polymer is in a globular conformation.

The pole does not exist (desorbed state): When there is no pole, one has to study the expansion of $\varphi(s)$ for small $s - \omega$ where ω is the value of the largest branch point, and $\omega = u$. It is convenient to use the shift theorem for Laplace transforms and write

$$\varphi(n) = e^{un} \mathcal{L}^{-1}[\varphi(u + s)] \tag{46}$$

The desired expansion of $\bar{\varphi}(s) \equiv \varphi(u + s)$ around $s \approx 0$ can be found after a straightforward computation. We used the Mathematica package to do that.

The inverse Laplace transform of the leading term in the expansion is given by

$$\varphi(n) \sim \frac{1}{\sqrt{u}\,\sinh[w\sqrt{u}] - c\cosh[w\sqrt{u}]}\frac{e^{un}}{\sqrt{\pi n}} \tag{47}$$

The denominator in the pre-factor should be positive since $\varphi(n)$ describes a positive quantity (the partition function). Indeed, the condition that the pole does not exist is given by $\tanh[w\sqrt{u}] - \frac{c}{\sqrt{u}} > 0$ which after multiplication by $\sqrt{u}\cosh[w\sqrt{u}]$ becomes exactly the term in the denominator.

The form of the asymptotic $\varphi(n)$ approximation indicates that the polymer is not adsorbed any longer. The $\sqrt{n}$ term in the denominator is the factor that one expects for a polymer near an impenetrable surface. The exponential term just indicates that the majority of the polymer is in the $z > w$ region and each monomer acquires the e^u Boltzmann factor.

The force is given by

$$f \sim \sqrt{u}\,\frac{1 - \frac{c}{\sqrt{u}}\tanh[w\sqrt{u}]}{\tanh[w\sqrt{u}] - \frac{c}{\sqrt{u}}} \tag{48}$$

and is always positive (when this approximation is valid). The denominator is positive due to the condition that the pole does not exist. The numerator is positive due to the fact that both the tanh function and the $c/\sqrt{u}$ factor are smaller than one, which also holds for their product.[25]

By inspecting the sub-leading terms in the expansion of $\bar{\varphi}(s)$ one can see that the expansion is valid only if

$$w \ll n\sqrt{u} \tag{49}$$

Thus, the expansion is valid for long chains, large u, and small w.[26] Note that for a fixed (large) n and a fixed u this condition becomes less and less valid as w is increased, until the condition turns into an equality. This implies that the asymptotic analysis for large n does not hold when w becomes too large. When w is too large the membrane can retrieve the polymer. Likewise, if u is too small, the gel is too "weak" to detach the polymer from the membrane.

There are two situations in which the force above is independent of w, leading to a plateau-like behavior. Firstly, the plateau clearly appears for very large values of u since both the numerator and the denominator approach 1. Secondly, if $\tanh[w\sqrt{u}] \approx 1$ the numerator and the denominator clearly cancel. This happens when

$$\frac{1}{\sqrt{u}} \ll w \tag{50}$$

In both cases the force is independent of w and the value of the plateau force is given by

$$f \sim \sqrt{u} \tag{51}$$

Interestingly, exactly the same analysis applies if one considers the $u \to \infty$ limit, where the polymer length is kept constant (not necessarily very large). For every fixed w there is a critical value $u_*(w)$ such that when $u > u_*(w)$ the pole is lost, and the above discussed approximations hold. As $w \to 0$ one has $u_*(w) \approx c/w$ which indicates that the critical value is very large for small w. For $w \to \infty$ one has $u_*(w) \approx c^2$ which is a number of order one. This suggests that when the gel is very close to the membrane it cannot easily detach an adsorbed polymer. However, when the distance increases it is much easer to do this.

VI. THE PHASE DIAGRAM

Now we are in a position to refine the definitions of the two states introduced previously. When the partition function has the pole, the polymer is strongly absorbed onto the membrane. While the gel can pull on the polymer, if the pole is present, the gel does not have enough strength to rip it off. This means that the polymer stays always close to the membrane and the length of the extension of the polymer from the membrane is controlled by the value of the pole. We call this state an adsorbed state. When the pole is not present, the gel has the potential strength needed to remove the polymer from the surface of the membrane. However, one cannot say automatically that the polymer is in a desorbed state. The fate of the polymer is decided by the distance between the polymer and the membrane. If the distance is not too large the gel can pull the polymer from the membrane, but for too large distances it cannot. There is a critical distance which depends on the length of the polymer. Ultimately, as discussed before, for very large distances the system acquires a hidden pole in the branch-cut integral $\varphi_\gamma(n)$ and the polymer becomes adsorbed again.

Figure 3 depicts the phase diagram of the system. Two combinations of parameters are useful in this context: $\lambda \equiv c/\sqrt{u}$ and the product cw. These two parameters describe the relative strengths of the gel versus the membrane, and the relative distance of the gel from the membrane measured in units of c^{-1}. For $\lambda > 1$ the pole is always present and the polymer is always adsorbed, regardless of the value of wc (phase "I" in the diagram). For $\lambda < 1$ there are two phases: the adsorbed one for $wc < \lambda \tanh^{-1}[\lambda]$ (phase "II") and another phase where $wc > \lambda \tanh^{-1}[\lambda]$ denoted by "III".

One has to be careful with the interpretation of phase III. If w is very large then one approaches the situation when the gel is absent, where the polymer is always adsorbed. In fact, the partition function of the zeroth order problem has a pole. Thus, not the entire phase III represents a desorbed state.

However, there is a region within phase III that can be characterized as desorbed. The analysis of the long chain (equivalently large u) in Section V D suggests that this happens when

$$\lambda \ll wc \ll \frac{\vartheta}{\lambda} \tag{52}$$

leading to the existence of the plateau. We postulate that such existence is an indicator of a truly desorbed state. Thus, phase III can be split into two regions depending on whether the force plateau exists (IIIa) or not (IIIb). Also, depending on the parameters that defined the system, the order of the two points marked by P_1 and P_2 in the figure can change and the size of the phase IIIa can shrink further.

VII. NUMERICAL RESULTS

The analytic analysis and the suggested phase diagram are supported by numerical tests. Figure 4 shows that the pulling force always increases with u regardless of the value of w. The analytic approximations capture the behavior correctly in their respective regions of validity (small versus large u regions). Note that in the asymptotic (large u) limit all curves have to merge into one universal curve where $f \sim \sqrt{u}$.

Figure 5 shows that the force exerted by a single polymer decreases with the distance between the gel and the membrane. As u is increased, the condition for the pole existence is valid for a broader range of w. This leads to the appearance of the plateau predicted by the analytic analysis. The plateau appears only if u is sufficiently large. The natural question in this context is whether one can expect appearance of the plateau when the length of the polymer is increased. An intuitive expectation is that very long polymers should reduce their energy by leaving the membrane for the gel region. Interestingly, this happens only if the pole is not present in the partition function. Figure 6 shows this clearly. All curves decay in an exponential like manner. Our interpretation is that the polymer stays attached to the membrane very closely. When the pole is not present the situation changes, as shown in Fig 7. Our interpretation of the figure is that very short polymers stay absorbed onto the membrane, while long polymers can lower their energy by leaving the membrane and occupying the gel region.

So far the analysis has been made without considering that u changes due to the fact that the concentration of the gel increases as w becomes larger. Figure 8 depicts the effects of the concentration change on the pulling force. We have chosen parameters that do not spontaneously result in any plateau (the pole is always present). There are always two effects working against each other, (i) the fact that the force decreases with w, and (ii) that it increases with u (concentration increase). It is not entirely clear what happens when the two effects compete against each other. The plot shows that effect (ii) can dominate over effect (i). From the small u approximation one can easily show that the slope of the force around $w \approx 0$ is proportional to $3/R - 2c$. The sign of

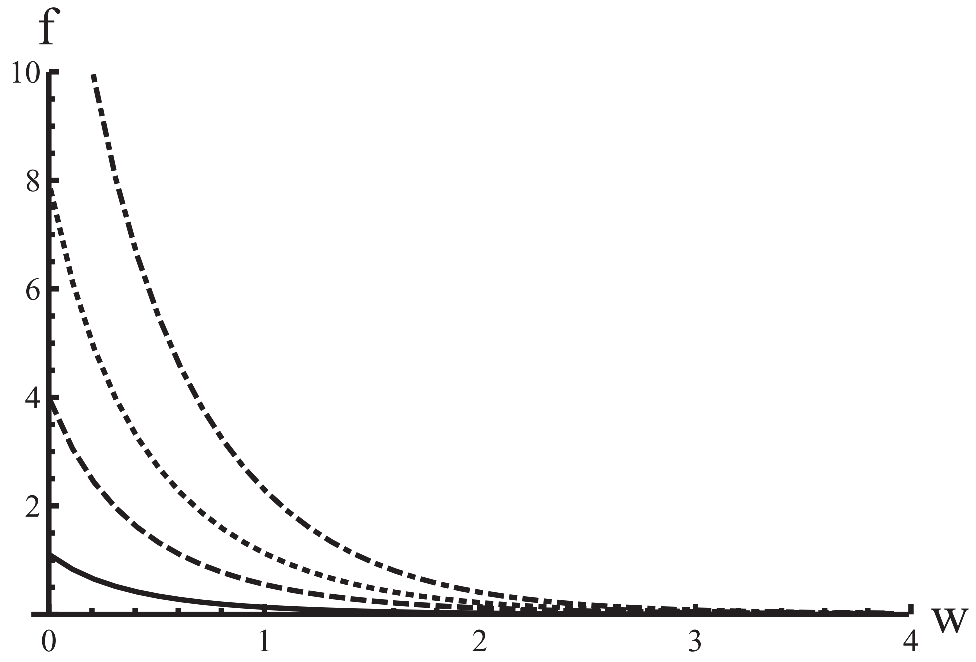

FIG. 6. The pulling force decreases with w. The force is plotted as a function of w for fixed values of $c = 1$ and $u = 0.5$. For such choice of c and u parameters there is always a pole since $\tanh[w\sqrt{u}] < 1 < c/\sqrt{u}$. The curves depict the pulling force for several values of n: $n = 1$ (the full line), $n = 4$ (the dashed line), and $n = 8$ (the dotted line), $n = 16$ (dash-dot). All curves decay in an exponential-like fashion. The force plateau is absent.

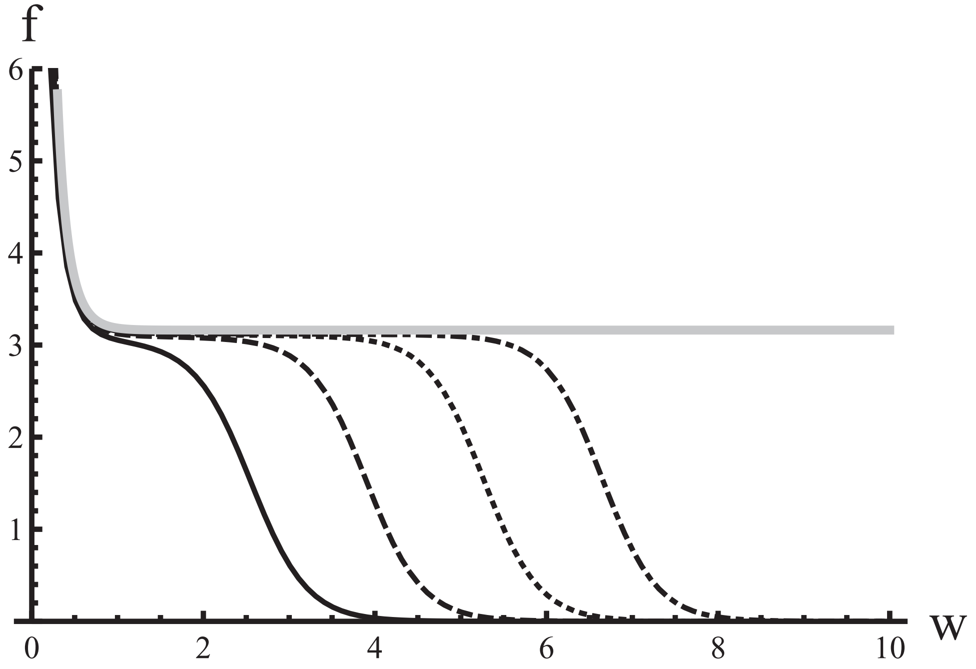

FIG. 7. The pulling force decreases with w. The force is plotted as a function of w for fixed values of $c = 1$ and $u = 10$. Such a choice makes the existence of poles dependent on the value of w since the condition $\tanh[w\sqrt{u}] < c/\sqrt{u} < 1$ has to be valid. The curves depict the pulling force for several values of n: $n = 1$ (the full line), $n = 1.5$ (the dashed line), and $n = 2$ (the dotted line), $n = 2.5$ (dash-dot). All curves decay in an exponential-like manner. The force plateau is present but very weak for short chains, and it lasts longer for longer chains. The gray curve depicts the force approximation.

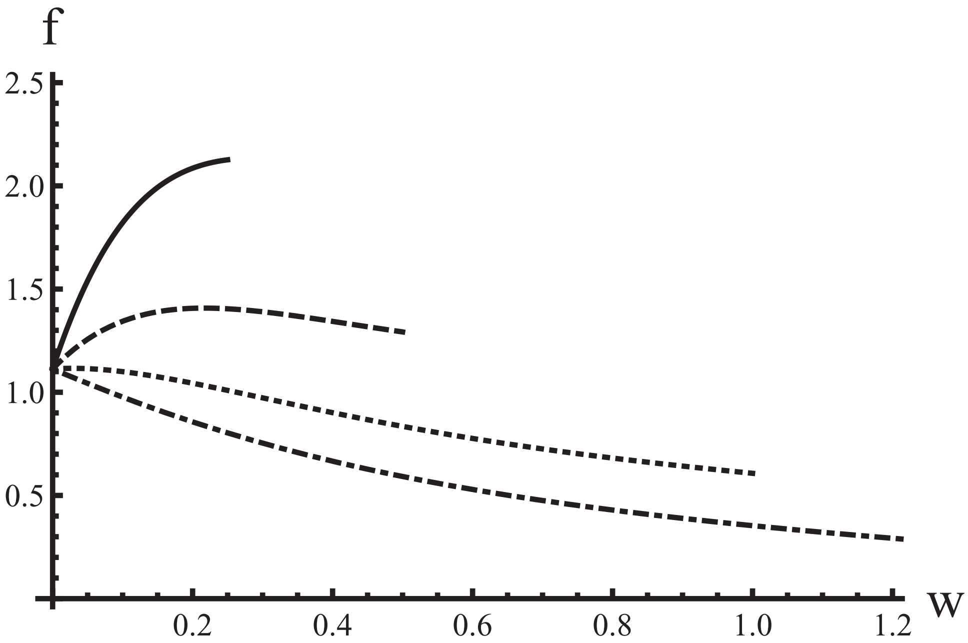

FIG. 8. The pulling as a function of w with u adjusted to keep the correct monomer concentration as $u(w) = u_0(1 + 3w/R)$. All plots are made with $c = 1$ and $u_0 = 0.5$. For small values of w the pole should always be present. The curves depict forces for various values of R: $R = 0.25$ (the full line), $R = 0.5$ (the dashed line), and $R = 1$ (the dotted line), and $R = 2$ (dash-dot). For every curve there is an upper limit of $w \sim R$ which is imposed by the geometry of the problem. For small vesicle sizes the force increases in the $w \approx 0$ region.

this quantity determines whether the force initially increases or not, and which effect dominates. This clearly depends on the radius of the spherical shell and the polymer-membrane adsorption strength c.

Figure 8 shows that the force at $w = 0$ gives a correct order of magnitude for the force. If the pulling force increases with increasing w, it does so in a mild manner, always staying within the same order of magnitude. The decrease is always exponential-like.

VIII. CONCLUSIONS

Here we presented an approach to estimate how the pulling force generated by a gel internalized in a spherical shell depends on key parameters that describe the system, most importantly the concentration of polymers C_0, the length of the polymer n, and the distance between the surface of the gel and the membrane w.

The key result of the paper is the Laplace transform of the expression for the pulling force with regard to the polymer length. The expression is too complicated for analytic analysis. We obtained several analytical approximation of the inverse Laplace transform in various regions of the parameter space, giving an analytical estimate for the pulling force. Most importantly, the exact expression for the pulling force has been found for the situation when the gel starts contracting ($w = 0$). It has been verified that the approximative equations are correct by comparing them with numerical results (obtained by numerically integrating the Fourier-Mellin formula). Furthermore, the numerical analysis showed that the pulling force at $w = 0$ defines roughly the order of the magnitude of the pulling force for all w. In fact, it was shown that the pulling force exhibits a plateau, i.e., there is an interval in w in which the pulling force stays constant. The plateau appears only if u is sufficiently large, or if the polymer is sufficiently long. Our interpretation is that the gel detaches the polymer from the membrane for the duration of the plateau. It is likely that the entropic price is paid by moving the monomers into the low potential region. These results have been presented in the form of a phase diagram.

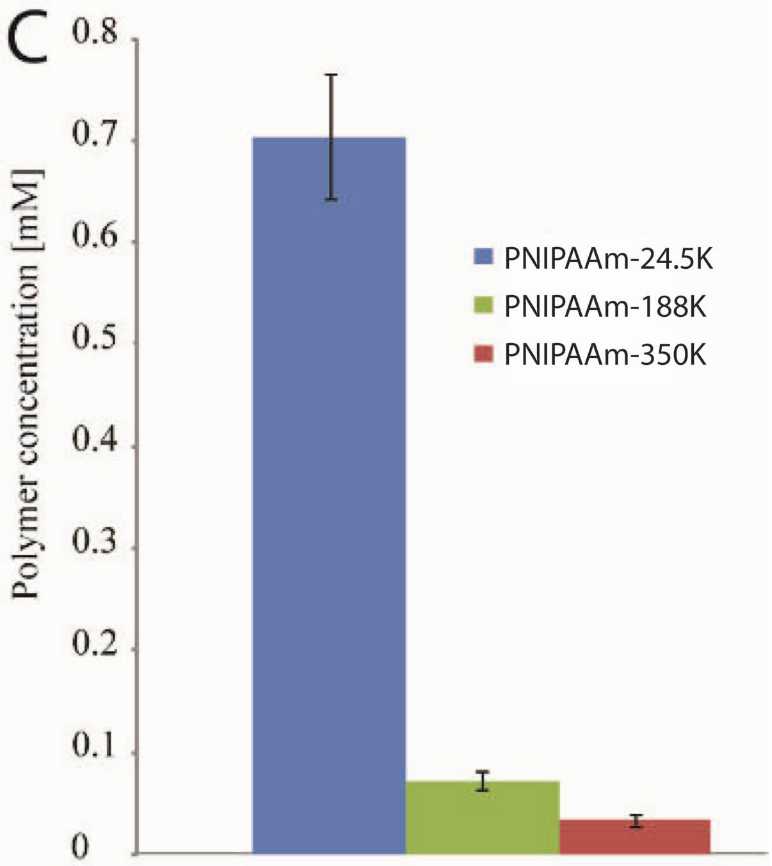

FIG. 9. Critical (minimal) polymer concentrations required to cause membrane deformations and pull nanotubes from a vesicle membrane upon hydrogel formation and contraction. Each bar represent the average obtained from measurements on six individual vesicles. Three polymers of different molecular weight were used. PNIPAAm-24.5K: Mol. weight 24500, PNIPAAm-188K: Mol. weight 188000, PNIPAAm-350K: Mol. weight 350000.

To qualitatively verify the theoretical findings we employed the experimental setup described initially in Section I B. The typical minimal force f_* needed to pull a nanotube is known to be $k_B T f_* / \kappa \sim 10pN$.[27] By investigating when $f \geq f_*$ it is possible to predict theoretically in which situations pulling should be observed, at least in a very qualitative terms. In particular, motivated by the experimental findings, we analyzed for which combinations of the polymer concentration C_0 and the chain length n the condition $f(C_0, n) \geq f_*$ is valid.

In principle, the fact that the force depends on the parameter w complicates the analysis somewhat. However, as discussed in the previous section, the order of the magnitude of the force is given roughly by the expression for the pulling force at $w = 0$. Thus at the qualitative level it is sufficient to work with the force formula evaluated at $w = 0$: $f_0 \equiv f(w = 0)$. It has been shown that for short and long chains the zero distance force f_0 is proportional to $C_0\sqrt{n}$ and $C_0 n$ respectively. From the requirement $f_0 = f_*$ it can be concluded that for short polymers $C_* \propto n^{-1/2}$, while for long polymers $C_* \propto n^{-1}$. These scaling laws confirm that indeed the critical polymer concentration is always a decreasing function of n.

The results of this analysis are supported by the experimental observations. We found that the outcome of an attempted pulling process strongly depends on the values of the injected polymer concentration and the polymer chain length. In particular, if the injected concentration of polymers is above (below) a certain threshold C_* the pulling occurs (does not occur).

The experiments indeed confirms the theoretical prediction that C_* is decreasing with increasing polymer length. In Fig. 9 the minimal concentrations of the polymers required to cause nanotube formation, are displayed for three polymers of increasing molecular weight. Thus qualitatively, the figure depicts C_* as a function of N. In the figure, all concentrations are expressed in units of mM. The error bars in Fig. 9 indicate that the concentration threshold for the same polymer fluctuates somewhat.[28]

The theoretical setup can be extended in order to obtain a more detailed description of the problem. For example, it should be possible to consider realistic membrane shape deformations on one hand, and more realistic polymer-gel interaction description on the other. A related challenge is to design alternative experiments to simulate the pulling action of a polymer on the lipid membrane in greater detail.

ACKNOWLEDGMENTS

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APPENDIX A: EXPERIMENTAL SETUP

In our own previous work we designed a model consisting of giant unilamellar vesicles (GUVs) connected to multilamellar vesicles (MLV), and a synthetic, water soluble polymer internalized by microinjection.[29] We succeeded in generating an artificial cytoskeleton[30,31] and formed compartments,[32,33] by manipulating synthetic polymers inside GUVs. Specifically, the following systems have been reported by us and other groups: a poly(ethylene)glycol/dextrane aqueous two-phase system (ATPS),[34] the application of agarose gels,[31] poly-N-isopropylacrylamide (PNIPAAm) or poly-ethylene dioxythiophene (PEDOT) polymer systems.[35,36]

We found PNIPAAm to be a versatile and functional material for the purpose of artificial cell design. It is a thermoresponsive lower critical solution temperature (LCST) polymer with the ability to reversibly contract significantly above its transition temperature of 32 °C. We had used PNIPAAm in several studies in the past.[37,38] However, in these studies we did not observe any polymer-membrane interaction, which might be due to relatively low concentration of the polymer employed.

We then introduced a PNIPAAm copolymerized with vinyl ferrocene (VFc) as a more hydrophobic component to assure better polymer contracting properties inside GUVs. Performing those experiments, as expected, we observed distinct polymer-membrane interactions during compartment formation. Interestingly, after repeating experiments with unmodified polymer, but at higher concentrations, we observed that unmodified PNIPAAm also affects the membrane.

These findings strongly suggest that the hydrophobic ferrocene moiety just facilitates the polymer-membrane interaction, under certain conditions the polymer can interact with the membrane on its own. The tendency to affect the membrane seems to be an intrinsic property of the polymer. The ferrocene moiety is not essential for the pulling process.

Controlled nanotube generation inside vesicles is difficult to achieve experimentally and the exact nature of the PNIPAAm-bilayer interaction is currently unknown. It is very challenging to design experiments that could illuminate how the pulling mechanism operates on the molecular level.

1. Chemicals

Soybean lecithin (polar lipid extract) was purchased from Avanti Polar Lipids and used as a starting material to create GUV- MLV pairs, using the modified Criado and Keller dehydration/rehydration procedure.[39] All experiments were carried out in a physiological buffer solution (PBS), pH 7.8. Three PNIPAAm samples of different molecular weights were investigated. Polymer PNIPAAm-24.5K: $M_W = 19000 - 30000 g/mol$, Sigma Aldrich, Stockholm, Sweden. Polymer PNIPAAm-188K: $M_W = 188000\ g/mol$, Polymer Source Inc., Montreal, Canada, and Polymer PNIPAAm-350K: $M_W = 350000\, g/mol$, Scientific Polymer Products (SPI), Ontario, USA. To prepare polymer solutions of desired concentrations, we assumed for polymer PNIPAAm-24.5K an average M_W of 24500 *g/mol*. The polymers have been diluted in PBS buffer to a final concentration of $C_0 = 20\, mg/ml$.

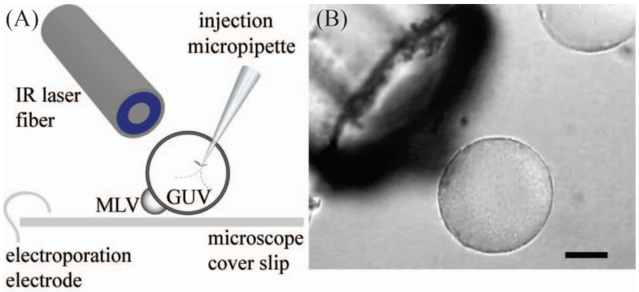

FIG. 10. (A) Schematic experimental setup. For polymer injection, a micropipette is inserted into a giant vesicle after electroporating the membrane to open a pore. One electrode is in the sample bath, and the other inside the glass microneedle. The glass pipette is connected to a pressure injection pump. The needle is retracted after each injection, and the polymer-containing vesicle is heated by the IR laser through an optical fiber. (B) An optical micrograph showing the IR heating fiber close to a multilamellar vesicle. Scale bar: $10\mu m$.

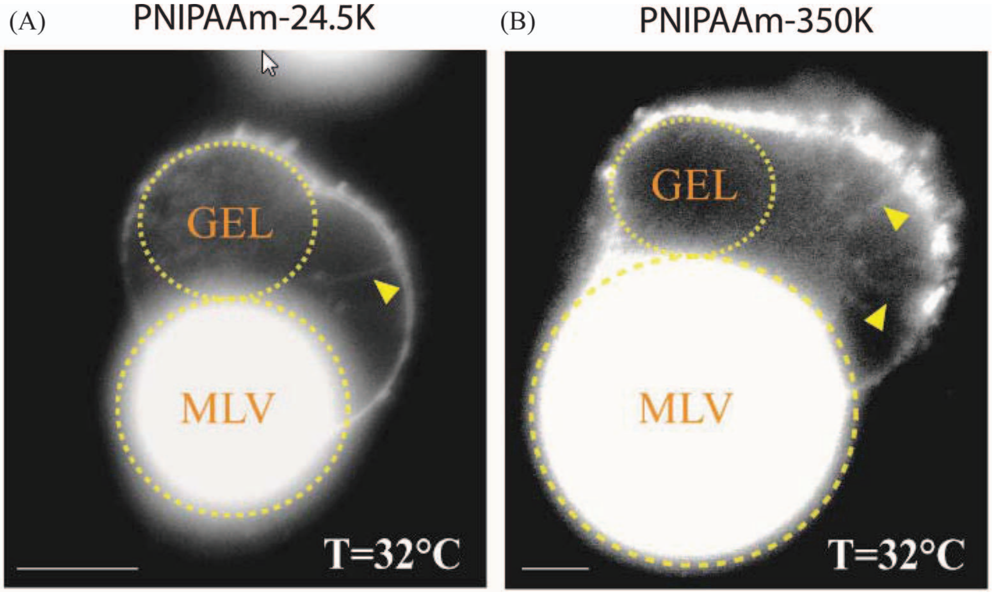

FIG. 11. PNIPAAm-membrane interactions visualized by means of fluorescence microscopy for the polymers of lowest (A) and highest (B) molecular weight. In the images, the positions of the multilamellar vesicle, and the gel compartment are emphasized. Yellow arrows point to some of the formed nanotubes. Scale bars: $10\mu m$.

2. Single vesicle heating

An in-house-built infrared (IR) laser microheating system consisting of a 5W, 1470nm (IR-B) semiconductor diode laser (Seminex HHF-1470-6-95) with an 8A power supply (4308 LaserSource, Arroyo Instruments) was used to heat individual vesicles. The setup is depicted in Fig. 10. The IR radiation was supplied to the sample through an end-polished 50 μm (core diameter) 0.22NA multimode optical fiber (Ocean Optics).

3. Microscopy

Imaging was performed under a Leica DR-IMB differential interference contrast and optical fluorescence microscope (Objective 40x 1.25 0.75 OIL). Most of the experiments have been performed without membrane dye, observing the membrane deformations and protrusions solely in the bright field. The shape changes induced by polymer PNIPAAm-350K where most pronounced, very likely due to the high molecular weight of this polymer. However, several experiments with dyed membrane (FM1-43 membrane stain, Invitrogen, Stockholm, Sweden) have been performed for polymers PNIPAAm-24.5K and PNIPAAm-350K in order to enhance visualization, as shown in Figure 11.

APPENDIX B: DETERMINING INTERACTION THRESHOLD CONCENTRATIONS

For the experiments, polymers PNIPAAm-24.5K, PNIPAAm-188K, and PNIPAAm-350K in PBS were injected into individual lipid vesicles at room temperature, below the lower critical solution temperature (LCST). The detailed injection protocol is described elsewhere.[40] Successively, small amounts of polymer were added to the vesicle to increase the polymer concentration inside the vesicle. Starting with a vesicle of a given radius R_0 filled only with PBS, one injects an approximately equal volume of polymer solution of known concentration into the vesicle. After each injection, the laser heating was switched on to heat the polymer solution in the vesicle above the LCST, and vesicle shape changes were monitored. The procedure was carried out until polymer-membrane interactions and membrane shape changes were observed. By measuring the vesicle radius under the assumption of spherical geometry, the final (minimal) concentration necessary for the interactions to occur first was determined. The occurrence of membrane shape change was used as indicator that the polymer interacts with the membrane.

After n injection steps the concentration of injected polymer in the vesicle ρ_n, and the vesicle radius R_n are related by

$$\rho_n = \rho_0 \left[1 - \left(\frac{R_0}{R_n} \right)^3 \right] \tag{B1}$$

where R_0 is the radius of the vesicle before injection and ρ_0 is the concentration of the polymer in the injection micropipette, used for injection ($\rho_0 = 20\, mg/ml$ for all polymers). Note that with repeated injections, the concentration in the vesicle approaches ρ_0. Each gel contraction process is initiated at a given ρ_n, which implies that $C_0 = \rho_n$. R_n have been measured by image analysis using the National Institutes of Health Image J software.

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[26] Note2, we used the Mathematica software to establish that the series has a form of $\bar{\varphi}(s) \approx A_0/\sqrt{s} + A_1 + A_2\sqrt{s} + \mathcal{O}(s)$. This implies that A_1 term has to be omitted from the analysis since it corresponds to the delta function term. The expansion is valid if the first term is much larger than the third term. The ratio between the third term and the first term is given by $ws/\sqrt{u}$. The condition in the text follows by requiring that this ratio is much smaller than 1.

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