Sensing viruses by mechanical tension of DNA in responsive hydrogels

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The rapid worldwide spread of severe viral infections, often involving novel modifications of viruses, poses major challenges to our health care systems. This means that tools that can efficiently and specifically diagnose viruses are much needed. To be relevant for a broad application in local health care centers, such tools should be relatively cheap and easy to use. Here we discuss the biophysical potential for the macroscopic detection of viruses based on the induction of a mechanical stress in a bundle of pre-stretched DNA molecules upon binding of viruses to the DNA. We show that the affinity of the DNA to the charged virus surface induces a local melting of the double-helix into two single-stranded DNA. This process effects a mechanical stress along the DNA chains leading to an overall contraction of the DNA. Our results suggest that when such DNA bundles are incorporated in a supporting matrix such as a responsive hydrogel, the presence of viruses may indeed lead to a significant, macroscopic mechanical deformation of the matrix. We discuss the biophysical basis for this effect and characterize the physical properties of the associated DNA melting transition. In particular, we reveal several scaling relations between the relevant physical parameters of the system. We promote this DNA-based assay for efficient and specific virus screening.

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I. INTRODUCTION

Modern means of transportation, civil aviation traffic in particular, effect extremely rapid global spreading of diseases [1, 2], contrasting the much slower spreading dynamics by traveling fronts, for instance, during the Black Death in Europe [3]. Concurrently, new infectious diseases keep emerging constantly, driven by human or ecological reasons [4], while disease-causing microorganisms are developing various forms of multiple drug resistance [5]. This development puts considerable strain on modern health care systems, requiring rapid, reliable, and specific diagnosis of infectious agents.

There exist a number of modern techniques to detect viral and bacterial pathogens. However, most of these methods require considerable time and resources. Thus, for the detection of bacteria typical techniques include the polymerase chain reaction and bacterial culture tests [6]. For viruses, on which we focus in this work, the detection methods include electrochemical [7], optical [8], surface plasmon resonance [9], and biosensor devices [10, 11]. Some of them reveal a high single-virus sensitivity and high selectivity to the virus type.

Several successful examples of viral detection by biochemical and biological techniques have indeed been reported. One of them is the macroscopic swelling of a polymeric acrylamide hydrogel, that is cross-linked by specially designed and folded ssDNA molecules, upon specific binding of influenza viruses [12, 13]. As demonstrated in that experiment, upon binding of a specific H5N1 influenza strain to the aptamer-containing hydrogel, which coats the surface of a quartz crystal microbalance biosensor, the linkages of DNA aptamers incorporated in the hydrogel become disrupted and the entire gel structure swells measurably. This highly specific and sensitive detection method for aptamer-based sensors has a number of advantages, as compared to the viral antibody-coated sensors, which are widely implemented for rapid detection of viruses, see, for instance, the assessment in Ref. [14]. Biosensor setups implementing surface plasmon resonance platforms based on antibody-antigen interactions were also shown to be efficient for a selective detection of various influenza, hepatitis B, and HIV viruses [15]. Surface plasmon resonance detection of avian influenza strains with a selectively-binding DNA aptamer immobilized directly on the sensor surface was developed in Ref. [16], combined with the a dot blot assay for a visual detection of viruses in tracheal swab samples.

Applications for use in local health care centers or even as mobile diagnostic tools require the miniaturization of the detection device, should provide a real-time signal without a prior amplification step, be easy to use, guarantee reproducible signals—and be relatively inexpensive. Physical instead of biochemical and biological techniques may indeed lead the way towards novel diagnosis methods. Thus, a relatively inexpensive and compact atomic force microscope setup to quickly and relatively cheaply test for bacteria and their response to drugs was recently proposed [17].

Could we come up with a method to detect viruses via a physical signal, for instance, a mechanical contraction of a matrix such as a responsive polyelectrolyte hydrogel, simply based on molecular interaction of the matrix with the surface of the virus shell? In what follows, from extensive computer simulations and statistical mechanical calculations we demonstrate that viruses may cause

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Figure 1: Schematic of ssDNA-virus binding with the definition of model parameters. Red and blue monomers on the shell correspond to attractive and neutral patches on the "raspberry" surface of the viral capsid. We show one of two ssDNA fragments of a partially denatured, linear DNA (green), at its extremities we indicate intact dsDNA. A real chain configuration as obtained in simulations for \( l_{\text{ss}} = 100\sigma \), \( p = 1/2 \), \( R = 6\sigma \), and \( \epsilon_A = 4k_BT \) is shown. This corresponds to a strong adsorption limit with a progressive wrapping of the flexible ssDNA chain around the attractive sphere. The shell is composed of a spiral running from the pole of the sphere along its surface, with red-blue monomers positioned according to the fraction \( p \). See text.

II. VIRUS-INDUCED DNA MELTING AND TENSION FORMATION

In the established thermodynamic models of DNA melting an alternating sequence of double-helical and denatured segments of different length form a partially molten DNA \([18, 22]\). Once a denaturation bubble is nucleated after overcoming a free energy barrier \( F_s \) associated with the cooperativity parameter \( \Omega = e^{-F_s/(k_BT)} \approx 10^{-5} \), base-pairs unzip (and zip close again) sequentially. DsDNA can be stabilized by some DNA binding cations (protamine, alkaline earth cations) and large ligands \([22]\), cationic lipids and surfactants, crowding agents such as Ficoll-70 \([24]\), basic poly-peptides, and DNA-binding proteins (histones), as well as DNA-DNA attractive interactions \([25]\). Conversely, dsDNA is destabilized by DNA unwinding proteins (gene 32 protein) \([26]\), external DNA twist and super-coiling \([27, 28]\), and stretching \([29, 30]\), as well as by single-strand DNA binding proteins and intercalators \([31]\).

The generation of an entropic force upon melting of pre-stretched, linear DNA fibers was demonstrated previously. Thus, for highly oriented dense DNA fibers, pre-stretched by picoNewton forces, the thermally or chemi-
ically induced melting transition of double-helical DNA was shown to trigger macroscopic changes of the fiber length. This melting-induced fiber contraction can reach up to 70-90% in such mechano-chemical studies, solely due to the entropically favored shrinking of the molten segments \( [32, 33] \); the highly flexible ssDNA segments have a much smaller equilibrium end-to-end distance compared to the much stiffer dsDNA fragments \( [35] \). Depending on the exact conditions of the solution (salt concentration, temperature, etc.) and the degree of torsional freedom, DNA entropic forces can indeed reach 10 to 40 pN per single DNA molecule in the fiber.

How do viruses come into play? The electrical charge of viruses was already studied in the 1920ies \( [36] \). Today we know that the external surface of the viral capsid, the protein-based shell of viruses, for a number of virus species features strongly non-uniform distributions of electric charges \( [35, 40] \). DNA binding to such shells can thus be based purely on electrostatic interactions. For instance, upon infection by an influenza virus, highly cationic haemo-glutinin HA glycoproteins domains, that form protrusions on the viral surface, anchor to negatively charged sialic acid receptors on the host cell surface \( [11, 12] \). A number of modern anti-flu drugs impede the viral infection proliferation via preventing these electrostatic contacts from forming.

In such a scenario, the DNA-virus binding affinity, the elastic parameters of DNA, and the energy difference between the molten and double-helical states of DNA are all delicately sensitive to the salt concentration and temperature of the ambient solution. For instance, in the range of 0.01 to 0.2 Molar of monovalent salt the DNA melting temperature \( T_m \) exhibits a logarithmic dependence on the salt molarity of the solution \( [13] \), leveling off at very large salinities \( [14] \). The electrostatic repulsion of interwound ssDNA strands becomes more pronounced at lower salt, thus effectively reducing \( T_m \). The effects of electrostatic interactions onto the thermodynamics of the DNA melting transition near a charged interface were analyzed in Refs. \( [45, 46] \).

Without external forces, the electrostatically driven adsorption-desorption transition of unconstrained polyelectrolyte chains such as DNA onto oppositely charged curved surfaces has been examined in detail theoretically \( [47, 48] \) and by computer simulations \( [49] \). The scaling laws for the critical adsorption transition were obtained experimentally as functions of polyelectrolyte chain-surface adhesion strength, salt conditions, surface curvature, and chain stiffness \( [50] \). To tackle such a transition for patchy curved surfaces and adsorbing polymers, as considered here numerically, remains a challenge.

Apart from these solution-sensitive, direct electrostatic attractions between DNA and the surface of the virus, there exists an alternative method to effect binding between ssDNA and the virus capsid. Namely, functionalized, chemically engineered viral shells can bind both dsDNA and ssDNA with different propensity via chemical linkers. For instance, ssDNA can bind better to viral shells covered with ssDNA-binding proteins, as used by viruses to dock to their host cells \( [41, 42] \). Thus, by various chemical and biochemical methods, the binding of ssDNA to virus shells may be effected experimentally. Using biochemical linkers, the ssDNA binding may indeed be rendered specific to certain virus types such as influenza, norovirus, HIV, or herpes. At the same time the binding affinity may reach relatively high values such that the bonds will not dissociate over fairly long timescales.

The presence of viruses can thus favor the (partial) melting of DNA chain. How can we combine the DNA-virus system with a hydrogel matrix? Hydrogels \( [51, 52] \) are extensively used in both industrial and medical applications, for instance, for tissue engineering purposes. These cross-linked polymeric materials feature a highly responsive behavior to various external stimuli such as temperature \( [53] \), solvent quality, pH as well as for detection of various substances \( [54, 55] \). The volumetric changes of up to 100 times in some hydrogels are reported \( [52] \) due to electro-osmotic swelling in low-salt solutions (cation accumulation). Viscoelastic hydrogels such as agarose feature a number of rubbery characteristics \( [56] \).

We assume that in the hydrogel individual DNA chains are supported in a pre-stressed, almost linear configuration, and that they are aligned in parallel, as sketched in Fig. 2. Perpendicular to their longitudinal axis, the DNA chains occupy a square or hexagonal lattice. We further assume that after adding viruses to the solution, each square or triangular “elementary cell” contains a virus particle. Thus, on average each virus is associated with one or two DNA double-helices, or two to three ssDNA strands after partial denaturation of the DNA chain, compare Fig. 1. Given the realistic parameters we use in our quantitative analysis below, this means that each ssDNA strand has sufficient accessible area to
bind to the surface of the virus capsids, without significant overlap with competing ssDNA segments. In what follows we consider the interaction of a single dsDNA strand with a given virus capsid. Due to the approximate independence of ssDNA binding to the virus capsids in all cells, we will then be able to upscale our results for the entire DNA bundle-virus assembly in the hydrogel. In this approach the position of the virus is fixed, reflecting the symmetry of the DNA-capsid configuration. We find that viral particles in the hydrogel-DNA system destabilize dsDNA and effect a macroscopic contraction of the hydrogel matrix.

III. RESULTS

A. DNA melting effects contraction of the hydrogel

As shown in our model configuration in Fig. 1, the surface of the virus is the distance \( z_0 \) away from the axis connecting the two end-points of the DNA that are fixed in the hydrogel. The separation between the axis of the DNA molecule from the center of the virus is thus given by \( \frac{z_0}{\sigma} = (z_0 + R) \), where, for simplicity, the virus capsid is taken to be spherical with radius \( R \), and that it is centered with respect to the longitudinal mid-point of the DNA chain between its two extremities incorporated in the hydrogel (Fig. 2). In our DNA-virus pair, due to the binding affinity of ssDNA to the capsid the part of the double-helix close to the virus capsid will melt (Fig. 1). The entire DNA molecule is thus composed of two dsDNA segments and two ssDNA segments resulting from the molten middle part.

For now we concentrate on one of these ssDNA segments, whose length \( l_{ss} = l_b + 2l_f \), in turn, is made up of the portion \( l_b \) bound to the viral shell and the two vicinal, unbound ssDNA fragments of length \( l_f \) each of which connects the bound portion with the two intact dsDNAs. Once such a configuration is established, the resulting entropic strain will be transferred to the end-points of the DNA chain. Since the base-pair to base-pair distance is approximately 0.34 nm in dsDNA, and the phosphate-phosphate distance 0.7 nm in ssDNA, the maximal ssDNA length available for binding to the virus is approximately two times the length of the corresponding dsDNA, provided that the dsDNA fragments can untwist freely upon melting which may be achieved by the specific anchoring in the hydrogel or by adding a nick close to the extremities of the DNA chain.

In our simulations, already denatured ssDNA chains are equilibrated and their most probable configurations are analyzed. We distribute positive electric charges on the capsid such that they occupy an area fraction \( p \). The interaction free energy \( F \) with the virus capsid due to electrostatic binding between the DNA chain and the positively charged sites on the capsid as well as the resulting contraction force \( f \) acting on the chain ends is computed, for different virus radii \( R \), DNA separations \( z_0 \) from the virus surface, and ssDNA-virus attraction strengths \( \epsilon_A \). This attraction strength is measured for one monomer of the ssDNA chain that corresponds to a sphere of diameter \( \sigma = 4 \text{nm} \) accommodating \( \approx 12 \) base-pairs of the dsDNA or 6 unpaired bases of the ssDNA. The DNA melting transition necessary for ssDNA formation, triggered by the free energy gain from binding to the viral surface, is analyzed below as a function of these parameters.

B. Free energy, forces, and adsorption transition

The relaxation time to reach the equilibrium increases with the length of the simulated ssDNA and for decreasing ssDNA-virus attraction strength. For an ssDNA chain consisting of \( n = 101 \) monomers the equilibration takes typically \( \approx 10^6 \) simulation steps, corresponding to approximately 10 min on a 3 GHz workstation. For polymer chains of 201 and 401 monomers, the equilibration time takes \( \approx 3 \times 10^6 \) and \( \approx 10^7 \) simulation steps. Every point in the figures below is calculated as an average over at least \( 10^4 \) polymer configurations, after equilibration of the system.

It is natural to expect that for large DNA-virus capsid binding strengths the thermal fluctuations of both the ssDNA and dsDNA chain domains become suppressed. They are effectively pulled out by the binding-mediated force, \( f_A \), directed towards the viral particle. For different virus dimensions and DNA-virus separations, this force contains a geometric correction factor \( C \) and turns out to follow the simple law

\[
 f_A = C\epsilon_A/\sigma, \tag{1}
\]

see below for details. Appendix A contains further information on the model potentials used in the simulations that act between the chain monomers as well as between the polymer chain and the virus surface.

The total free energy of a partially molten DNA double helix is comprised of the sum of entropic and energetic contributions along the equilibrated chain, the interaction energy of the polymer chain with the virus surface \( U \), and the DNA melting free energy \( F_{\text{melt}} \). The DNA-virus attraction energy scales with the length of bound ssDNA

\[
 U = B(p)\epsilon_A l_b/\sigma. \tag{2}
\]

The constant \( B(p) \) accounts for multiple contacts that the chain monomers can establish with the attractive sphere monomers, where \( p \) quantifies the surface fraction of attractive binding spots on the virus, see below. The DNA melting free energy consists of the free energy cost for base-pair unstacking, \( \Delta F \), and the initiation free energy \( F_s \) for nucleation of a denaturation bubble,

\[
 F_{\text{melt}} = F_s + \Delta F l_{ss}/(6\sigma). \tag{3}
\]

For simplicity, all the DNA-related energies are assumed to be independent of the DNA base-pair sequence, its
GC content \[^60\], and, most crucially, the length of the ssDNA fragments. In the simulations presented below we use \(\Delta F = 0.3 - 0.5k_B T\) and \(F_s = 10k_B T\). The relatively small \(\Delta F\) values mimic a system away from equilibrium, where the values of \(\Delta F \sim 1k_B T\) are typically used.

The denaturation equilibrium of dsDNA and the fluctuation spectrum of ssDNA become altered by the ssDNA binding to the viral capsid. The optimal length of the molten DNA \(l_{SS}^{melt}\) is determined self-consistently from the minimum of the total free energy functional. As order parameter for the DNA adsorption transition we use the fraction of DNA base-pairs adsorbed to the viral shell,

\[
\theta = \frac{l_s}{l_{SS}}.
\] (4)

The position of the phase transition boundary crucially depends on the strength of the DNA-virus attraction, the DNA density in the bundle, scaling as \(1/[\pi(s/2)^2]\), and the virus dimensions, \(R\). It will be instructive to account for the maximal fraction of ssDNA, \(\theta_{\text{max}}\), to be adsorbed due to geometrical constraints of the system, see below. In this state, the flanking ssDNA fragments are fully stretched (strong adsorption limit). The value of \(\theta_{\text{max}}\) is a function of the virus size and the DNA-capsid separation.

We implement the (standard) dynamical criterion for adsorption of a ssDNA chain monomer to the virus. When a monomer stays in contact with the surface for more than 50% of the simulation time, it is considered adsorbed. We assume that a portion \(0 < p < 1\) of the spherical virus surface, composed of monomeric patches as indicated in Fig. 4, is attractive to ssDNA. Fig. 4 shows a typical configuration of the virus surface with adsorbed DNA. Generally, attractive monomers may form a single attractive patch or be distributed randomly on the surface, as implemented below. Another possibility is to form a structure of interconnected ridges mimicking a non-uniform distribution of attractive capsid proteins on the virus surface. Note that for partially attractive surfaces, the ssDNA monomers proximal to both attractive and neutral capsid monomers are equally counted adsorbed by the above criterion.

The contractile force \(f\) along the DNA axis acting on the dsDNA extremities connected to the hydrogel is due to both entropic ssDNA fluctuations tending to coil up the chain and (partial) adsorption to the virus capsid. To find \(f\) for a fixed length \(l_{SS}\) of ssDNA and for different overall DNA end-to-end distance \(y_0\), we compute the binding energy \(U(y_0)\) using the weighted histogram analysis method (WHAM) \[^61\]. The latter is a particular implementation of the umbrella sampling method. Then, we evaluate the force as

\[
f = -\frac{d}{dy_0}[U(y_0) + F_{\text{melt}}(y_0)] = k_y \delta l.
\] (5)

Here the elastic constant \(k_y\) for the displacement \(\delta l\) of the DNA ends varies in the range \(k_y \sim 0.1...1k_B T/\text{nm}^2\) for different DNA densities and for the Young modulus of a hydrogel, \(E \sim 20\text{kPa}\). This value of \(E\) is due to other polymeric components of the hydrogel supporting the incorporated, regular lattice of DNA interacting with viral particles \[^62\].

For a typical DNA density \((s \sim 70...150\text{nm})\), we compute the cross-section area per DNA in our cell model as \(S \approx \pi(z_0 + R)^2\). Then, the microscopic contraction of one DNA in the cell via the Young modulus can be related to the relative contraction of the entire material via

\[
\frac{\delta l}{l_{SS}} \approx \frac{f}{E \pi(z_0 + R)^2}.
\] (6)

This contraction is triggered by ssDNA adsorption to the virus surface and represents the macroscopically measured quantity.

### C. Fixed ssDNA length

We now present the results of our extensive molecular dynamics computer simulations. To that end we first obtain the statistical behavior for the DNA-virus interaction for a fixed length of the available ssDNA fragment, before determining the optimal ssDNA length self-consistently. We note that the relatively high initiation barrier \(F_s\) for DNA bubble formation prohibits the creation of short molten stretches of ssDNA. Only longer ssDNA fragments are stabilized by binding to the viral capsid.

We find that the fraction \(\theta\) of adsorbed segments increases with the adsorption strength \(\epsilon_A\) once a critical value \(\epsilon_{A}^*\) is exceeded. After this transition the amount of adsorbed ssDNA segments increases up to a saturation plateau given by \(\theta_{\text{max}}\), see Fig. 3. As mentioned above, the geometry of our setup influences the shape of this transition, in particular, the distance \(z_0\) between
the central DNA axis and the surface of the capsid, see below. Due to the transition as a function of the adsorption strength, the standard sigmoidal DNA melting curve $\theta(T)$ known from thermal melting in our adsorption-induced melting scenario acquires a kink. According to Fig. 4 the transition of $\theta = \theta(\epsilon_A)$ appears to be of second order. For large viruses and strong ssDNA-virus attraction, nearly all chain monomers are adsorbed and non-adsorbed ssDNA fragments are therefore fully stretched. For a fixed DNA-virus separation $z_0$, the fraction $\theta$ increases with the capsid radius $R$ as the overall number of available attractive patches on the viral shell increases. In the limit of strong binding affinity $\epsilon_A$, the fraction $\theta$ saturates to the geometry-dependent value $\theta_{\text{max}}(R, z_0)$. We observe that smaller viral particles naturally require larger attraction strength for the onset of the denaturation adsorption and yield smaller fractions of bound ssDNA bases, as shown in Figs. 5 and S1 (Supplementary Material).

Interestingly, the decrease of the fraction of non-adsorbed ssDNA bases with the attraction strength fulfills the scaling relation

$$\frac{\theta_{\text{max}} - \theta}{\theta_{\text{max}}} \sim \frac{k_B T}{\epsilon_A}, \quad (7)$$

for sufficiently large values of $\epsilon_A$. This universal dependence is illustrated in the inset of Fig. 3. The scaling relation (7) is fully consistent with the extension of a polymer chain in a limit of strong stretching forces. This follows from the relative chain extension $\tau/L_0 = \coth[f \sigma/(k_B T)] - 1/[f \sigma/(k_B T)] \approx 1 - 1/[f \sigma/(k_B T)]$ of a worm-like polymer at large applied forces $f \sigma/(k_B T) \gg 1$. Here the chain contour length is $L_0 = (n - 1)\sigma$. As the stretching force is due to ssDNA adsorption to the viral capsid, we have $f = \epsilon_A/\sigma$ and $(L_0 - \tau)/L_0 \sim (\theta_{\text{max}} - \theta)/\theta_{\text{max}} \sim k_B T/\epsilon_A$.

In line with our expectations, the distribution of the chain monomers adjacent to the attractive viral capsid surface becomes strongly localized at larger binding affinities, see Fig. 4. For the case $\epsilon_A = 2k_B T$ the width of this distribution is indeed very narrow. This distribution significantly broadens and its maximum shifts away from a monomeric distance from the capsid surface when $|\epsilon_A|$ decreases. This is an obvious tradeoff between entropic and enthalpic effects when $\epsilon_A$ is comparable to thermal energy.

A natural question to ask is whether, similar to the thermal melting transition, the sharpness of the binding-induced DNA melting transition increases with DNA length. We study the effect of ssDNA length in Fig. S2, observing that shorter chains require larger adsorption strengths to initiate the DNA-virus binding (at a constant DNA-virus distance). We also observe faster saturation to the geometry-limited value $\theta_{\text{max}}$. However, the transition does not appear sharper for longer ssDNA molecules: approximately the same number of adsorbed polymer segments is detected at the onset of ssDNA binding at the critical attraction strength $\epsilon_A = \epsilon_A^\ast$.

We also find that the critical value $\epsilon_A^\ast$ decreases for larger radii $R$ of the capsid, as shorter DNA-virus separations need to be bridged by the molten DNAs, thus facilitating the adsorption process, see Fig. 4. In comparison, the critical $\epsilon_A^\ast$ for different $R$ with same $z_0$ is nearly identical (not shown). This indicates small effects of the shell surface curvature on the onset of the adsorption transition. For adsorption strengths well above the adsorption transition, in contrast, the surface curvature effects are vital because they regulate the number of sites available for adsorption for a given chain length $l_{ss}$ and shell-DNA separation $z_0$, as seen from Fig. 3.

At a critical DNA-DNA separation $s^\ast = s^\ast(R)$ the length of the ssDNA segment is insufficient to allow adsorption to the capsid. The critical attraction strength at this adsorption-desorption transition of the ssDNA naturally diverges, as shown in Fig. 5. Well above the add-
sorption transition (e.g., at relatively small $s$ values) the data reveal a distinct scaling of the critical adsorption strength with the capsid radius,

$\epsilon^*_A(R) \sim s/R = 2z_0/R + 2.$ \hfill (8)

This asymptote, shown in the inset of Fig. 5, reveals the geometric competition between the DNA-virus separation $s$ and the radius $R$.

In Fig. 6 we present the results for the fraction $\theta$ of bound ssDNA monomers with varying fraction $p$ of attractive, randomly-distributed capsid monomers. For larger ssDNA-virus attraction strengths $\epsilon_A$, smaller $p$ values are sufficient to trigger the DNA adsorption, that is, the parameter $p$ of the surface coverage by attractive capsid monomers is complementary to the adsorption energy $\epsilon_A$ per monomer $\sigma^*$. The DNA adsorption reveals an apparent second-order continuous transition in the variable $p$. It is thus natural to introduce the generalized parameter $p\epsilon_A$ and to re-examine relation (7) obtained above for the uniformly-attractive sphere. We observe that the fraction of unbound ssDNA monomers exhibits the analogous scaling behavior, substituting $p\epsilon_A$ for $\epsilon_A$.

D. Optimal ssDNA length and hydrogel contraction

In the previous subsection, we studied the adsorption transition at a fixed ssDNA length. Physically, this length is determined self-consistently from the competition of DNA-virus attraction and DNA melting free energy, as detailed here.

As the DNA length $l_{ss}$ of the overall ssDNA segment is varied, we find an optimal length $l_{ss}^{\text{opt}}$, that corresponds to the minimum of the total free energy. With progressing DNA adsorption the attractive energy $U$ decreases almost linearly for short ssDNA and appears to saturate for longer chains. This slower increase of $|U|$ is due to a self-repulsion of the segments already adsorbed on the sphere. The melting energy cost grows linearly with the length of molten DNA, see Eq. (3) and Fig. S3.

In Fig. S4 we show the optimal ssDNA length for three energy differences $\Delta F$ between ssDNA and dsDNA. The melting transition only takes place if the total free energy in the molten-adsorbed state is lower than that in the helical-desorbed state. This defines the minimal bubble size when DNA virus-induced melting becomes energetically beneficial. Below a critical adsorption strength $\epsilon_A^*$, no DNA melting takes place and $l_{ss}^{\text{opt}} = 0$. For $\epsilon_A > \epsilon_A^*$, the value $l_{ss}^{\text{opt}}$ starts to grow from a finite value with $\epsilon_A$, as shown in Fig. S4. This jump-like behavior is indicative of a first-order transition, in contrast to the continuous change in $\theta$ presented in Fig. 6. Smaller $\Delta F$ values favor bubble formation and an earlier onset of DNA opening, and thus shift the equilibrium towards the molten DNA state.

The dependence of the optimal ssDNA length on the model parameters defines the onset of a longitudinal contraction in the system. Starting from the adsorption strength $\epsilon_A^*$, the contraction force per DNA increases nearly linearly with the ssDNA-virus adhesion strength, Fig. 7. The contraction force acting on the DNA ends follows the linear scaling with $\epsilon_A$ given by Eq. (1). For larger $\Delta F$ values the equilibrium length of the ssDNA decreases, while its effect on the gel contraction becomes stronger.

Collecting our previous results we arrive at the main conclusion of this work, the relative contraction $\delta l/l_{ss}$ of the hydrogel. According to Eq. (9), this relative contraction $\delta l/l_{ss}$ scales linearly with the contraction force $f$ and is inverse-proportional to the Young modulus $E$. According to Fig. 7 the force $f$ is approximately proportional to the attraction strength $\epsilon_A$, thus confirming Eq. (1). The right axis in Fig. 7 shows the corresponding relative contraction $\delta l/l_{ss}$ effected by a single ssDNA-virus interaction within one of the ‘elementary cells’ of
our setup. Accordingly, for the value $E = 20\text{kPa}$ of the hydrogel Young modulus, this would give rise to a contraction of $3\ldots5\%$. Assuming that at least two ssDNA per ‘elementary cell’ contribute, the contraction of the entire hydrogel would reach almost $10\%$. This, however, is a conservative estimate with respect to the relatively high value for the Young modulus $E$ that we chose here. Using softer hydrogels, $E$ can easily be reduced considerably, thus leading to a much stronger response to the viral binding. This macroscopic hydrogel contraction is thus immediately detectable.

IV. CONCLUSION

Based on extensive computer simulations and statistical analyses we explored the thermodynamic properties of DNA melting induced by binding of single-stranded DNA to viruses and the effected longitudinal tension build-up in the involved DNA chains. In particular, we determined how a preferable adhesion of ssDNA fragments to the surface of the virus shifts the DNA melting equilibrium and alters the character of the DNA melting transition. We found the critical adsorption strength of ssDNA chains to the attractive viral shell under the conditions of DNA confinement in an elastically-responsive polymer matrix of a hydrogel. The statistical properties of the partially molten and partially adsorbed DNA chains obtained from computer simulations are in line with the theoretical expectations. We found several scaling relations for the fraction of adsorbed DNA, the critical adsorption strength, and, most importantly, the relative shrinkage of the suspending hydrogel.

As a proof of concept we demonstrated that the presence of viruses in a liquid solution may be detected directly by mechanical response of a hydrogel, transduced by pre-stretched DNA chains suspended in the hydrogel. These DNAs partially melt and thus expose single-stranded DNA, that itself binds to the virus shell. This binding can, in principle, be made specific for certain types and sizes of viruses. All ingredients are fairly inexpensive to produce, and such a setup can easily be miniaturized. We believe that this setup is a good candidate for mobile use or for use at local health care centers. Alternatively to measuring the mechanical deformation of the hydrogel, one could also envision optical signals due to either DNA melting (similar to molecular beacon setups [64]) or strong local hydrogel deformation. The binding to DNA located in separate domains of the hydrogel can be made specific to certain virus types by biochemically specific functionalized units on the virus.

We believe that the effects determined herein may form an alternative basis for miniaturized and inexpensive viral detection under non-clinical conditions.

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Appendix A: Simulations scheme

We consider the adsorption of ssDNA onto an attractive surface of a viral particle in a simplified model. The ssDNA is modeled by Lennard-Jones (LJ) particles interconnected by finitely extensible nonlinear elastic (FENE) springs of the potential

$$U_{\text{FENE}}(r) = -\frac{k}{2}\sigma^2 \ln \left(1 - \frac{r^2}{r_{\text{max}}^2}\right), \quad (A1)$$

where $k$ is the FENE spring constant and $r_{\text{max}}$ is the maximum allowed separation between neighboring monomers. Excluded-volume interactions between the monomers are given by the short-ranged truncated LJ repulsion,

$$U_{\text{LJ}}(\epsilon, r) = \begin{cases} 4\epsilon[(\sigma/r)^{12} - (\sigma/r)^{6}] + \epsilon, & r < 2^{1/6}\sigma \\ 0, & \text{otherwise} \end{cases} \quad (A2)$$

Here, $r$ is the monomer-monomer distance, $\sigma$ is the monomer diameter, and $\epsilon$ is the strength of the potential. We set the parameters to $k = 30$, $r_{\text{max}} = 1.5\sigma$, and $\epsilon = 1$. The monomer size is $\sigma = 4\text{nm}$, close to the Kuhn length of a highly flexible ssDNA. In contrast to dense DNA fibers [34], here we can neglect DNA-DNA interactions because the intermolecular separations exceed the diameter of a typical virus, $2R \sim 50-100\text{nm}$, and the electrostatic forces between individual DNA chains are well screened.

Performing simulations of a free chain, we checked that the effective ssDNA persistence length in this model agrees well with the known estimate of $l_p = 1-4\text{nm}$ [63, 66], and the chain gyration radius follows the Flory law $R_g^2 \sim n^{3/5}$ for an excluded-volume/self-avoiding polymer as function of the number $n$ of monomers.

The spherical viral shell of radius $R$ is modeled by a densely packed assembly of LJ beads of size $\sigma$. A finite fraction $0 < p < 1$ of the monomers, distributed either in a random or ordered fashion on the viral surface, is attractive for ssDNA segments in their vicinity. The ssDNA-virus attraction is modeled via the same spherically symmetric LJ potential,

$$U_{\text{PV}}(r) = U_{\text{LJ}}(\epsilon_A, r), \quad (A3)$$

but with a larger cutoff-distance $r^* = 2.5\sigma$ to ensure the existence of an attractive potential branch at larger distances and with varying attraction strength $\epsilon_A$. The
where \( m \) is the monomer mass, \( \xi \) the friction coefficient, \( \mathbf{v}_i \) the monomer velocity, and \( \mathbf{F}^R \) represents zero-mean Gaussian noise with component-wise \( \delta \)-correlation, 
\[
\langle \mathbf{F}^R(t) \mathbf{F}^R(t') \rangle = 6 \xi k_B T \delta_{ij} \delta(t - t').
\]

The positions of the two polymer ends, \((0, 0, z_0)\) and \((0, y_0, z_0)\), and of the virus center \( \mathbf{r}_V = (0, y_0/2, -R) \) are fixed, see Fig. 1. In the simulations, we set \( m = 1 \), \( \xi = 1 \), and \( k_B T = 1 \). The equation of motion is integrated using the velocity Verlet algorithm \cite{67} with a time step \( \Delta t = 0.01 \).

[1] V. Belik, T. Geisel, and D. Brockmann, Natural Human Mobility Patterns and Spatial Spread of Infectious Diseases, Phys. Rev. X 1, 011001 (2011); L. Hufnagel, D. Brockmann, and T. Geisel, Forecast and control of epidemics in a globalized world, Proc. Natl. Acad. Sci. USA 101, 15124 (2004).

[2] B. Davoudi, J. C. Miller, R. Meza, L. A. Meyers, D. J. D. Earn, and B. Pourbohloul, Early Real-Time Estimation of the Basic Reproduction Number of Emerging Infectious Diseases, Phys. Rev. X 2, 031005 (2012).

[3] J. V. Noble, Geographic and temporal development of plagues, Nature 250, 726 (1974).

[4] K. E. Jones et al., Global trends in emerging infectious diseases, Nature 451, 996 (2008).

[5] A. J. Alain, Resistance to antibiotics: are we in the post-antibiotic era? Arch. Med. Res. 36, 697 (2005); R. S. Sellar and K. S. Peggs, Management of multi-drug-resistant viruses in the immuno-compromised host, Brit. J. Haematol. 156, 559 (2012).

[6] C. D. Sibley, G. Peirano, and D. L. Church, Molecular methods for pathogen and microbial community detection and characterization: Current and potential application in diagnostic microbiology, Infection, Genetics, and Evolution 12, 505 (2012).

[7] F. Patolsky et al., Electrical detection of single viruses, Proc. Natl. Acad. Sci. USA 101, 14017 (2004).

[8] B. Brandenburg et al., Imaging Poliovirus Entry in Live Cells, PLoS. Biol. 5, e183 (2007).

[9] S. Wang et al., Label-free imaging, detection, and mass measurement of single viruses by surface plasmon resonance, Proc. Natl. Acad. Sci. USA 107, 16028 (2010).

[10] N. S. Hobson, I. Tothill, and A. P. F. Turner, Microbial detection, Biosens. Bioelectr. 11, 455 (1996).

[11] M. Schoening and A. Poghosian, Recent advances in biologically sensitive field-effect transistors (BioFETs), Analyst 127, 1137 (2002).

[12] R. Wang and Y. Lia, Hydrogel based QCM aptasensor for detection of avian influenza virus, Biosens. Bioelectr. 42, 148 (2013).

[13] J. Liu et al., Aptamer-incorporated hydrogels for visual detection, controlled drug release, and targeted cancer therapy, Anal. Bioanal. Chem. 402, 187 (2012).

[14] D. Li et al., A nanobeads amplified QCM immunosensor for the detection of avian influenza virus H5N1, Biosens. Bioelectr. 26, 4146 (2011).

[15] J. H. Lee et al., Highly sensitive localized surface plasmon resonance immunosensor for label-free detection of HIV-1, Nanomedicine 9, 1018 (2013), and references cited therein.

[16] R. Wang et al., Selection and characterization of DNA aptamers for use in detection of avian influenza virus H5N1, J. Virol. Methods 189, 362 (2013).

[17] G. Longo et al., Rapid detection of bacterial resistance to antibiotics using AFM cantilevers as nanomechanical sensors, Nature Nanotech. 8, 522 (2013).

[18] D. Poland and H. A. Scheraga, Phase Transitions in One Dimension and the Helix-Coil Transition in Polyamino Acids, J. Chem. Phys. 45, 1465 (1966).

[19] Yu. S. Lazurkin, M. D. Frank-Kamenetskii, and E. N. Trifonov, Perspectives report: Melting of DNA: Its study and application as a research method, Biopolymers 9, 1253 (1970).

[20] J. SantaLucia Jr., A unified view of polymer, dumbbell, and oligonucleotide DNA nearest-neighbor thermodynamics, Proc. Natl. Acad. Sci. USA 95, 1460 (1998).

[21] Y. Kafri, D. Mukamel, and L. Peliti, Why is the DNA Denaturation Transition First Order?, Phys. Rev. Lett. 85, 4988 (2000).

[22] D. Jost and R. Everaers, A Unified Poland-Scheraga Model of Oligo- and Polynucleotide DNA Melting: Salt Effects and Predictive Power, Biophys. J. 96, 1056 (2009).

[23] J. M. McGhee, Theoretical calculations of the helix-coil transition of DNA in the presence of large, cooperatively binding ligands, Biopolymers 15, 1345 (1976).

[24] Y. Liu et al., Crowding effect on DNA melting: a molecular thermodynamic model with explicit solvent, Phys. Chem. Chem. Phys. 14, 15400 (2012).

[25] A. G. Chernyav and A. Kornyshev, DNA melting in aggregates: impeded or facilitated?, J. Phys. Chem. B 109, 13024 (2005).

[26] D. E. Jensen, R. C. Kelly, and P. H. von Hippel, DNA "melting" proteins. II. Effects of bacteriophage T4 gene 32-protein binding on the conformation and stability of nucleic acid structures, J. Biol. Chem. 251, 7215 (1976).

[27] J. H. Jeon, J. Adamcik, G. Dietler, and R. Metzler R, Supercoring Induces Denaturation Bubbles in Circular DNA, Phys. Rev. Lett. 105, 208101 (2010).

[28] A. Kabakcioglu, E. Orlandini, and D. Mukamel, Supercoil formation in DNA denaturation, Phys. Rev. E 80, 010903(R) (2010).

[29] M. Rief, H. Clausen-Schaumann, and H. E. Gaub, Sequence-dependent mechanics of single DNA molecules, Nature. Struct. Biol. 6, 346 (1999).

[30] A. Hanke, M. G. Ochoa, and R. Metzler, Denaturation Transition of Stretched DNA, Phys. Rev. Lett. 100, 018106 (2008).

[31] K. R. Chaurasia, T. Paramanathan, M. J. McCauley, and M. S. Williams, Biophysical characterization of DNA binding from single molecule force measurements, Phys.
R. G. Winkler and A. G. Cherstvy, *Mechanochemical study of conformational transitions and melting of Li-, Na-, K-, and Cs-DNA fibers in ethanol-water solutions*, Biopolymers **34**, 897 (1994).

J. Piskur and A. Rupprecht, *Aggregated DNA in ethanol solution*, FEBS Lett. **375**, 174 (1995).

J. Schultz et al., *A mechanochemical study of MgDNA fibers in ethanol-water solutions*, Biophys. J. **66**, 810 (1994).

A. R. Khokhlov and A. Y. Grosberg, *Statistical Physics of Macromolecules*, American Institute of Physics, New York, (1994).

S. P. Bedson and J. O. W. Bland, *A Simple Method for Determining the Electrical Charge carried by Virus Particles*, Brit. J. Exp. Pathol. **10**, 67 (1929).

A. Siber, A. L. Bozic, and R. Podgornik, *Energies and pressures in viruses: contribution of nonspecific electrostatic interactions*, Phys. Chem. Chem. Phys. **14**, 3746 (2012).

http://viperdb.scripps.edu

A. L. Bozic and R. Podgornik, *Symmetry effects in electrostatic interactions between two arbitrarily charged spherical shells in the Debye-Hückel approximation*, J. Chem. Phys. **138**, 074902 (2013).

A. G. Cherstvy, *Electrostatic interactions in biological DNA-related systems*, Phys. Chem. Chem. Phys. **13**, 9942 (2011).

N. Arinaminpathy and B. Grenfell, *Dynamics of Glicoprotein Charge in the Evolutionary History of Human Influenza*, PLoS ONE **5**, e15674 (2010).

Y. Kobayashi and Y. Suzuki, *Compensatory evolution of net-charge in influenza A virus hemagglutinin*, PLoS ONE **7**, e40422 (2012).

C. Schildkraut and S. Lifson, *Dependence of the melting temperature of DNA on salt concentration*, Biopolymers **3**, 195 (1965).

R. Owczarzy et al., *Effects of sodium ions on DNA duplex oligomers: improved predictions of melting temperatures*, Biochemistry **43**, 3537 (2004).

A. Vairrub and B. M. Pettitt, *Accurate Prediction of Binding Thermodynamics for DNA on Surfaces*, J. Phys. Chem. B **115**, 13300 (2011).

J. Fuchs et al., *Salt Concentration Effects on Equilibrium Melting Curves from DNA Microarrays*, Biophys. J. **99**, 1886 (2010).

A. G. Cherstvy and R. G. Winkler, *Polyelectrolyte adsorption onto oppositely charged interfaces: unified approach for plane, cylinder, and sphere*, Phys. Chem. Chem. Phys. **13**, 11686 (2011).

R. G. Winkler and A. G. Cherstvy, *Strong and weak polyelectrolyte adsorption onto oppositely charged curved surfaces*, Adv. Polym. Sci. **255**, 1 (2013).

Q. Cao and M. Bachmann, *Polyelectrolyte adsorption on an oppositely charged spherical polyelectrolyte brush*, Soft Matter **9**, 5087 (2013); S. C. C. Nunes, T. F. G. G. Cova, and A. A. C. Pais, *A new perspective on correlated polyelectrolyte adsorption: Positioning, conformation, and patterns*, J. Chem. Phys. **139**, 054906 (2013); F. Carnal and S. Stoll, *Adsorption of Weak Polyelectrolytes on Charged Nanoparticles. Impact of Salt Valency, pH, and Nanoparticle Charge Density*, Monte Carlo Simulations, J. Phys. Chem. B **115**, 12007 (2011).

A. B. Kayitmazer et al., *Protein-polyelectrolyte interactions, Soft Matter** **9**, 2553 (2013).

O. Okay, *Macroporous copolymer networks*, Prog. Polym. Sci. **25**, 711 (2000).

O. Okay, *General properties of hydrogels, in “Hydrogel Sensors and Actuators”, G. Gerlach and K.-F. Arndt (eds.), Springer Series on “Chemical Sensors and Biosensors” 6*, 1 (2009).

I. Tokarev and S. Minko, *Stimuli-responsive hydrogel thin films*, Soft Matter **5**, 511 (2009).

C. Bilici and O. Okay, *Shape Memory Hydrogels via Misselar Copolymerization of Acrylic Acid and n-Octadecyl Acrylate in Aqueous Media*, Macromol. **46**, 3125 (2013).

K. Gawel et al., *Responsive Hydrogels for Label-Free Signal Transduction within Biosensors, Sensors** **10**, 4381 (2010).

M. Quesada-Perez et al., *Gel swelling theories: the classical formalism and recent approaches*, Soft Matter **7**, 10536 (2011).

E. Wischerhoff, N. Badi, J. F. Lutz, and A. Laschewsky, *Smart bioactive surfaces*, Soft Matter **6**, 705 (2010).

M. A. Cohen-Stuart et al., *Emerging applications of stimuli-responsive polymer materials*, Nature Mater. **9**, 101 (2010).

M. A. A. Barin, et al., *Characterizing the viscoelastic properties of thin hydrogel-based constructs for tissue engineering applications*, J. Royal Soc. Interface **2**, 455 (2005).

G. Khandelwal and J. Bhyravabhotla, *A phenomenological model for predicting melting temperatures of DNA sequences*, PLoS ONE **5**, e12433 (2010).

A. Grossfield, “WHAM: the weighted histogram analysis method”, version 2.0.7, http://membrane.urmc.rochester.edu/content/wham The WHAM algorithm to computing the contractile force is equivalent to a brute-force simulation of DNA adsorption at different end-to-end separations, when the molecule is subject to a parabolic potential $W$ that confines its ends, $W = k_W(\delta)^2/2$. In case of weak DNA-sphere adsorption, however, the WHAM method produces more reliable force estimates and it is therefore used throughout the paper.

For many hydrogels the stress-strain relations and the Young modulus are obtained from analysis of elastic deformations and ball indentation [59]. The Young modulus varies in the range $E = 0.01 \ldots 30 \text{kPa}$, depending on the gel cross-links density, its chemical composition, and temperature [54]. Typically, the modulus grows nearly linearly with concentration of cross-linked polymer chains. Typical values of 5-20 kPa are reported for the agarose gels at 0.5-1.5% polymer concentrations in the regime when gel stretching dominates over its bending. The compositions of hydrogels can include various polyelectrolyte chains in different proportions, including a double-stranded DNA (dsDNA).

Some deviations from this scaling for strong adsorption are due to the fact that in this case only a small number of polymer monomers are actually in tight contact with the surface. The monomers in polymers loops interconnecting these adsorbed links are however also counted as adsorbed as they are close to the surface. This gives rise to a higher fraction of adsorbed monomers and some deviation from the universal behavior [17] in the strong adsorption limit. Smaller $p$ values and larger adsorption strength are more efficient in binding ssDNAs to the capsid shells.
[64] G. Bonnet, O. Krchovsky, and A. Libchaber, *Kinetics of conformational fluctuations in DNA hairpin-loops*, Proc. Natl. Acad. Sci. USA **95**, 8602 (1998).

[65] H. Chen, S. P. Meisburger, S. A. Pabit, J. L. Sutton, W. W. Webb, and L. Pollack, *Ionic strength-dependent persistence length of single stranded RNA and DNA*, Proc. Natl. Acad. Sci. USA **109**, 799 (2012).

[66] C. Rechendorff, G. Witz, J. Adamcik, and G. Dietler, *Persistence length and scaling properties of single-stranded DNA adsorbed on modified graphite*, J. Chem. Phys. **131**, 095103 (2009).

[67] M. P. Allen and D. J. Tildesley, *Computer simulations of liquids* (Clarendon Press, Oxford, UK, 1987).