

Computer simulations of DNA packing inside bacteriophages: Elasticity, electrostatics and entropy

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There is now a considerable literature on computer simulations of DNA packaging inside bacteriophage capsids. While most studies have reached a semiquantitative or qualitative agreement with single molecule packaging and ejection studies, several quantitative answers are to date still lacking, needing either more accurate measurements or more realistic or difficult simulations. Here, I briefly review the outstanding questions in this field and report some new numerical results on DNA packaging inside the phi29 phage, modelled either as a capped spherocylinder or as a sphere with the same internal volume. These simulations include electrostatics and a realistic genome length, and contribute to seriously questioning the inverse spool model, which arises from a purely continuum mechanics view of the problem, and is still commonly adopted to describe the shape of the packaged genome.

Keywords: DNA phages; DNA packaging; computer simulations; Monte-Carlo simulations; single molecule experiments

AMS Subject Classification: 82C80; 92B99

1. Introduction

Arguably, the simplest example of genome organization in biological organisms is provided by the double-stranded (ds) DNA which is confined inside bacteriophages, the viruses which infect bacteria. DNA phages are an ideal minimal system to be studied, both for biologists and physicists. Biologically, these are the simplest kind of viruses: they are believed to function by taking advantage of the sheer pressure which the DNA inside them is subjected to, due to the high degree of packing, to be ejected into the cytoplasm of a host cell when infection takes place. Physically, this system only consists of a polymer, the negatively charged DNA, inside a convex hull, the phage capsid. As a result, this is an ideal model system to enhance our understanding of DNA in confined geometries, a topic of fundamental interest in biophysics: Due to the small number of components, models can be quite accurately solved and in principle we have the chance to quantitatively compare the theoretical and experimental answers to a number of questions. For instance, what is the shape of the DNA inside the capsid? What is the force needed to package the genome? Can we single out the various contributions due to electrostatics, elasticity and entropy in the experimentally measured force? Can we characterize the dynamics of packaging and ejection, *e.g.* in terms of rates and total packing or ejection times? What is the

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effect of the salt concentration in the buffer on the packaging force and dynamics? Is there any relation between packaging and phage maturation?

Experiments have attempted to answer these questions and they have provided us with a wealth of interesting data and observations to be rationalized theoretically [11,14,16,33–35]. For instance, single molecule techniques have allowed researchers to play thug of war with the molecular motors of a few selected capsids, and it has been shown that the force which these motors may exert is surprisingly large: *e.g.* in order to package the DNA inside phi29, a force of 50–60 pN is required [35]. More recently, a series of quantitative measurements of the dependence of the packaging force on phage identity and ionic strength has been published [11]. Sophisticated imaging electron microscopy techniques, not relying on icosahedral averaging, have also unveiled the structure attained by the first few layers of genome inside the bacteriophage ϵ 15 [16]. Finally, the physics of DNA ejection from a selection of bacteriophages, and especially its kinetics, have recently been considered in a series of accurate experiments [8,9,20,21]. A remarkable finding was that DNA ejection from phage λ could be completely or partially suppressed by increasing the osmotic pressure in solution or by adding multivalent counterions to the solution. The latter situation has recently been considered in numerical simulations of the DNA ejection problem as well [3].

As a result, we are now in a position to quantitatively compare the experimental and theoretical answer to the questions above. At the moment, we are at a point in which the agreement is qualitative or semiquantitative: quantitative agreement would probably require more elaborate theories. For instance, the order of magnitude of the packaging force predicted by most models is in the tens of pN range, which is the experimentally observed one, but the more recent and accurate experiments in Ref. [11] have shown that the existing calculations cannot quantitatively account for the steep increase in the packaging force with ionic strength in a monovalent salt buffer. Furthermore, the data reported in Ref. [16] seemingly support the inverse spool model, according to which the DNA is highly ordered inside the phage head. However, an increasing number of simulations, albeit typically neglecting electrostatic forces, is now being published, reporting striking and very significant deviations from the inverse spool model. Therefore, perhaps the simplest and oldest questions in DNA phage biophysics, *i.e.* what is the shape of the packaged DNA? is still to some extent controversial, in that it is still not clear what a typically accepted model of a semiflexible chain inside a small sphere predicts for the typical shape!

The focus of the present work is on computer modelling of the DNA packaging problem. The structure is as follows. In the next section, I will briefly review the existing literature in the field. Then, I will introduce a Monte-Carlo dynamical model, which we recently used to study the growth of a semiflexible polymer inside a soft vesicle, and which can be readily generalized to study the DNA packing process. I will apply this model to study the process of DNA packing inside the phage phi29, modelled either as a cylinder with spherical caps or as a sphere with the same internal diameter. DNA is modelled as a semiflexible self-avoiding polymer, interacting via an electrostatic Debye–Hueckel potential, suitable to describe the effective interactions in a monovalent salt buffer. The results suggest that within this coarse-grained model, by using commonly accepted values for the DNA persistence length and Debye–Hueckel length, the ordering inside phi29 may be smaller than typically assumed.

2. Review of the numerical literature on DNA inside phages

While biophysical theories to study DNA packing and ejection have quite a long history [7,12,13,25,26,30] (albeit these were mainly limited to an analysis of free energy losses and not of force curves), serious numerical simulations of the same problems have only started much

more recently. This is on one hand because in order to characterize thermodynamically the process of DNA loading into phages one needs to sample typical configurations of a strongly confined polymer. This is quite difficult as equilibration times in this situation are often prohibitively large for DNA molecules of tens of kilo-base pairs, as the phage DNAs are. Molecular dynamic simulations are also challenging as the times needed to study DNA ejections are in the several second range, which is a very large time for even coarse-grained simulations (a time step in these simulations may typically be 0.01–0.1 ns). Here, I restrict to a brief review of this simulation work. Readers interested in more analytical or semianalytical approaches may want to consult Refs. [25,26,31,32] and References therein.

Kindt *et al.* [18,38] were the first to study the thermodynamics of DNA packing, *i.e.* the free energy lost and force needed to package DNA inside a spherical hull. The model used was a coarse-grained one in which DNA was discretized as a semiflexible polymer, a chain of beads of size 2.5 nm each, and persistence length in the 50–100 nm regime. Two force fields were considered: one in which the polymer was self-repelling and another one in which it was self-attracting. It was found that in the case of self-attracting interactions the DNA inside the sphere started the packaging in a toroidal fashion, to attain a spool-like shape later on. The authors calculated the force acting on the last bead being packaged and found that it abruptly increases when the density of the DNA inside the phage approaches the values found in bacteriophages like phi29 and lambda (*i.e.* 40–50% in volume fraction).

After that, we considered in Ref. [23] the case of a self-avoiding flexible tube of thickness 2.5 nm and performed Monte-Carlo numerical simulations to compute the free energy loss during packing and the packaging force, again finding a value in the tens of pN range for the latter quantity. This calculation clarifies that the fact that the DNA has a finite thickness, by itself is enough to give rise to a strikingly large osmotic pressure inside the phage, or equivalently requires a strong molecular motor to pack dsDNA into a phage. In the framework we considered, the force can be seen as purely entropic, in that it only derives because as the density (or packing fraction) increases, progressively less configurations are allowed inside the capsid. This gives rise to a free energy (equivalently configurational entropy) loss, which when derived (with respect to the DNA packing fraction) yields the force curve. By definition, then, this calculation gives an estimate of the thermodynamic, or equilibrium, force – dynamic effects, which cannot be estimated in this way, might increase this value. In traditional theories, entropic contributions to the free energy loss and force curves in DNA packaging into phages were neglected: this calculation was the first one to challenge this view. The simulations in Ref. [23] were performed with pure self-avoidance, hence are equivalent to the ones in Ref. [18,38] with repulsive Lennard-Jones interactions. The configurations inside the phage were not arranged according to the ideal inverse spool model, a fact also found first with molecular dynamics simulations of the packaging of a stiff chain inside a spherical cavity [6]. More accurate molecular dynamics simulations have now been performed which have confirmed that (i) entropy plays a primary role in packing and that (ii) the inverse spool model needs at least considerable corrections in order to account for the non-idealities in the simulations [10,19, 27–29].

The dynamics of the packaging, and more recently of the ejection, of DNA inside and out from phages were first studied in Refs. [1,2]. It was found that the capsid shape had a major influence on the packaging and ejection dynamics. Interestingly, the results were different according to the flexibility of the polymer packed into the capsid. For flexible polymers, a sphere packs faster and ejects slower than an elongated capsid. As the polymer gets stiffer, the trend changes and for a polymer with a DNA-like elastic modulus a spherical capsid is the best shape to both pack and eject its genome. These studies also provided estimates for the dynamic effects during packing and ejection, and showed that there is a significant component in the force which is purely dynamic in origin. Furthermore, it was shown that even a simple model of a motor

as a grab-and-pull machinery is enough to produce pauses in the packaging process. These pauses were seen experimentally first in Ref. [35], and the mechanism leading to them could therefore be due to stochastic fluctuations in the packaging process alone. This interpretation has also been proposed in later simulations [10].

Other simulation papers on the DNA packaging process have recently been published [4,5,10,19,27–29,36]. Most of these are performed with life-like genome length with realistic geometries for bacteriophages. These simulations confirmed the finding that the shape of the packaged DNA was considerably less ordered than previously assumed on the basis of the experimental results. Given this, a question which has been asked is: why is the DNA ordered in reality, while it does not appear to be so in simulations? In Ref. [36], it was shown that simulations considering the fact that the molecular motor rotates the DNA during the packaging lead to enhanced order in the genome. In Ref. [10], other simulations were presented from which it appears that if a cylindrical protein core (present in some albeit not all phages) is added inside the capsid, then again the ordering increases. This finding is also confirmed in Ref. [27], where the electron micrographs which would arise from the simulated (and not very well ordered) DNAs are shown to be in semiquantitative agreement with experimental data. I have recently performed additional simulations [22] to systematically evaluate how much the (nematic) ordering of the DNA inside the capsid is affected by (i) ionic strength, (ii) identity of the DNA self-interaction (attractive vs. repulsive), (iii) capsid shape and (iv) capsid-DNA interaction. Ordering is mainly enhanced by elongated shapes and attractive self-interactions. Decreasing the ionic strength leads to stronger repulsion but, strikingly, less genomic ordering.

3. Model and methods

In this section, we present the algorithm which we have used to study DNA packaging. The potential used to model the DNA interactions comes from a large body of experiments aiming at establishing how to best approximate DNA as a fluctuating elastic polyelectrolyte (see, *e.g.* Ref. [37]). We consider a semiflexible polymer of persistence length ξ (fixed to 50 nm as appropriate for ds DNA), confined inside a convex hull of fixed geometry. We considered the case of phi29 hence two different capsid shapes: a cylinder capped by two hemispheres (sphero-cylinder geometry) or a sphere with the same internal volume, V . The chain is discretized as a series of N beads, of diameter σ , and links of length σ (we used $\sigma = 2.5$ nm as appropriate for hydrated ds DNA). The packing fraction of the polymer inside the hull is then $\phi = N\pi\sigma^3/6V$ (in phi29 ϕ is about 0.5).

The Hamiltonian characterizing a purely elastic self-avoiding polymer is:

$$\mathcal{H} = -K_b \sum_{i=1}^{N-2} \vec{t}_i \cdot \vec{t}_{i+1} + \sum_{i=1}^{N-1} \sum_{j=i+1}^N V_{\text{h.c.}}(|\vec{r}_i - \vec{r}_j|), \quad (1)$$

where $\{\vec{r}_i\}_{i=1,\dots,N}$ represent the positions of the N beads, $\vec{t}_i = \vec{r}_{i+1} - \vec{r}_i$ are the $N - 1$ links, $K_b = \xi k_B T$ and $V_{\text{h.c.}}(|\vec{r}_i - \vec{r}_j|)$ is a hard core potential which is infinity when $(|\vec{r}_i - \vec{r}_j|)$ is smaller than σ .

Electrostatic self-interactions are screened by the solvent, and are modelled via Debye–Hueckel theory. We consider the case of a monovalent buffer, which is typically NaCl in experiments with DNA phages. We have therefore considered the following Debye–Hueckel additional potential:

$$V_{\text{DH}} = \sum_{i=1}^{N-1} \sum_{j=i+1}^N \frac{\sigma^2 k_B T l_B}{a^2} \frac{\exp(-\kappa |\vec{r}_i - \vec{r}_j|)}{|\vec{r}_i - \vec{r}_j|}, \quad (2)$$

where k_B is the Boltzmann constant, l_B is the Bjerrum length (0.7 nm in water), a is the distance between two elementary charges along the polyelectrolyte (0.35 nm for DNA), and κ is the inverse Debye length, which is equal to $0.31/C$ nm, where C is the molar strength of the monovalent salt used in the buffer.

The calculations have been carried out by using a generalized three-dimensional Monte-Carlo dynamical algorithm (known as *kink-jump dynamics*) [24]. This couples trial local moves of the polymer and the vesicle to polymerization or depolymerization attempts, which consist in adding or deleting – with rates k_{on} and k_{off} , respectively – a monomer from one end of the chain, the other one being fixed (at the capsid entrance where the motor is located, for phi29). Trial local moves of the polymer are accepted according to the usual Metropolis criterion. Growth stops when we reach the required filling fraction for the polymer beads inside the capsid. (This method allows a better sampling of the chain properties under the strong confinement inside the capsid.) During one simulation time step, on average, we attempt to move each monomer in the polymer, and we also attempt to grow or shrink the polymer. This model has recently been used to study the growth of a semi-flexible polymer inside a soft vesicle in Ref. [24].

In order to characterize statistically the properties of the confined chain, with beads at positions $\{\vec{r}_i\}_{i=1,\dots,N}$, we also computed the tangents, $\{\vec{t}_i\}_{i=1,\dots,N-1}$, with $\vec{t}_i = (\vec{r}_{i+1} - \vec{r}_i) / (|\vec{r}_{i+1} - \vec{r}_i|)$. Averages may be done globally, or locally, in the latter case resulting in a spatial dependence of \vec{t} . These vectors define the matrices (Greek indices denote Cartesian components):

$$Q_{\alpha\beta} = \frac{3}{2} \left(t_\alpha t_\beta - \frac{\delta_{\alpha\beta}}{3} \right). \quad (3)$$

This tensorial order parameter is used in nematic liquid crystals to characterize the isotropic-to-nematic phase transition [17]. We name the largest eigenvalues (in modulus) of $Q_{\alpha\beta} N$ (for ‘nematic ordering’).

4. Results on phi29 packaging

In this work, I focus on a specific application of DNA packing inside the phi29 bacteriophage. Simulations performed with the same technique but addressing more fundamental questions in polymer physics, *i.e.* looking at the effect of the polymer persistence length on the ordering inside the capsid, will be discussed separately [22].

Figure 1 shows typical conformations of DNA inside phi29, modelled as either a spherocylinder or a sphere, with the same internal volume. The average degree of nematic ordering close to full packing in the two cases is 0.15 and 0.05, respectively (these values were obtained as an average over four runs each). For comparison, the value of the nematic order in the ordered phase is, in Onsager’s theory of lyotropic liquid crystals, in the range 0.25–1, so that the values of N in phi29 are quite low. Indeed, an inspection of the conformation qualitatively confirms that the order within the bacteriophage head is far from perfect, and different nematically ordered domains or spools coexist together. In the simulation leading to Figure 1, there are self-repulsive interactions between any two DNA segments, as appropriate for a physiological buffer with only monovalent salts in it. Attractive interactions do lead to a better ordering [10,18,22,38], and these could be induced by introducing multivalent counterions in the buffer – these will however not be considered in detail here. It is interesting to note that the slightly elongated spherocylinder capsid leads to an increased nematic ordering with respect to the spherical capsid. (Typically, the only parameter which is thought to impact on the physics of the packaged DNA is the volume fraction of the phage it occupies, which is the same by construction in the two geometries in our calculation.)

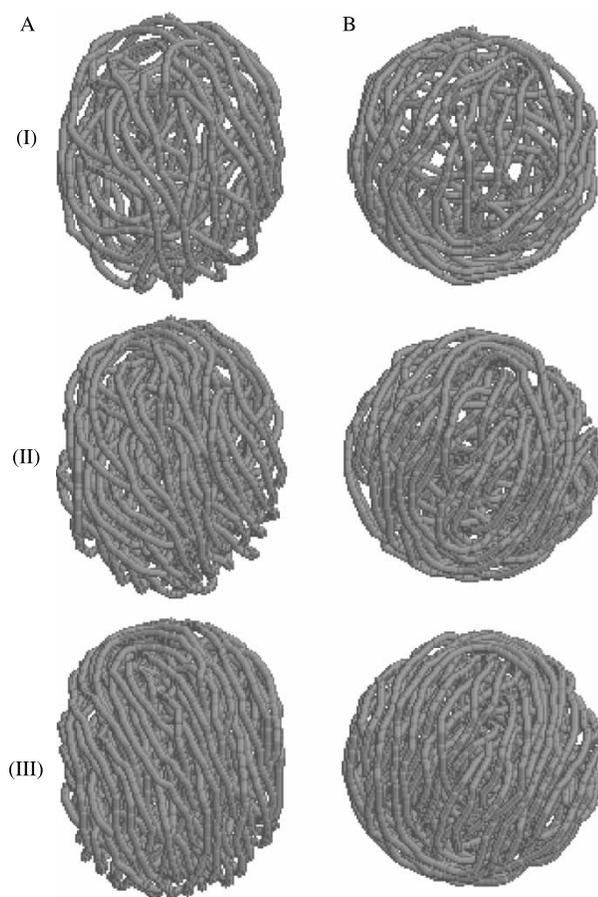


Figure 1. Typical configurations at various stages of the packaging process for DNA inside phi29, modelled as a spherocylinder (A) or a sphere (B). It can be seen that the arrangement is quite far from being perfectly ordered. Rows (I)–(III) refer to successive stages in the packaging process.

This theoretical result of a rather disordered genome organization within the phage is at first sight at odds with the experiments which are consistent with at least a few layers of highly structured genome. One could argue that electrostatic interactions between different segments of dsDNA, which are negatively charged, contribute to stiffen up the molecule to increase the ordering, and render simulations and observations more similar. To probe this possibility, we performed simulations with a polyelectrolyte with the charge separation typical of dsDNA [30], in a buffer containing monovalent counterions at a variable concentration. The comparison of two configurations (for intermediate packing) with small and large ionic strength is shown in Figure 2. These results qualitatively show that the amount of ordering does not increase with increasing repulsion. Quantitatively, we have performed simulations with Debye lengths equal to 0.75 and 1.75 nm, which respectively lead to values of N equal to 0.05 and 0.045.

That enhanced electrostatic repulsion does not lead to an increased order in the DNA conformation may be rationalized by noting that decreasing the concentration of salt, while it stiffens up the fibre locally, also increases its effective diameter. The DNA molecule thus tries to fill the space most effectively inside the phage and this leads to a loss rather than an increase in spool-like or nematic ordering. It would be nice to compare different electron micrographs

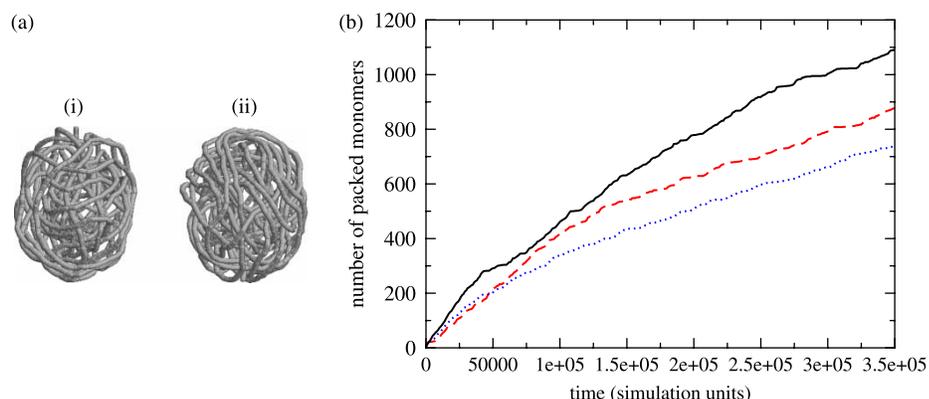


Figure 2. Effect of electrostatics: (a) two typical configurations at about 50% packing, for DNA packing inside a sphere – (i) and (ii) refer to simulations with Debye lengths equal to 0.75 and 1.75 nm, respectively and (b) packaged length vs. time (both in simulation units) for Debye length equal to 0.75 nm (solid line), 1.75 nm (long dashed line) and 2.5 nm (dotted line). Available in colour online.

of DNA inside phi29 or other isometrical phage capsids, for different ionic strengths of a buffer containing monovalent counterions, and to quantitatively test this prediction.

Our model may not lead to a realistic DNA dynamics as the packaged genome is grown inside the fibre instead of being packaged as in Refs. [1,2]. Close to full packaging it might however be realistic to assume that this mechanism corresponds qualitatively to polymer reptation and starts to mimic the physical dynamics. In any case, if we record the packaged length of the polymer inside the phage as a function of simulated times for both the geometries (Figure 3), the rate of change of these curves decreases if the force opposing the packaging is larger, and increases otherwise. By comparing the packaged length dynamics in the elongated and spherical model for the phi29 capsid, we observe that the DNA is packed more quickly into the spherical capsids, with respect to the more elongated one. This is in line with what was observed on the basis of hydrodynamic simulations of DNA packing into phages of different shapes and same internal volume in Ref. [1]: it is quite pleasing that our dynamics albeit somewhat artificial does reproduce this observation. Interestingly, a fine analysis of the length

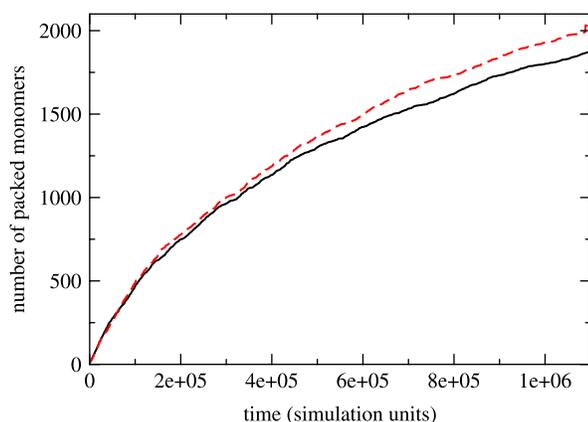


Figure 3. Packed length vs. time (both in simulation steps) for DNA inside phi29. The solid and dashed lines respectively refer to packaging inside a spherocylinder and a sphere (with the same internal volume). Available in colour online.

curves in Figure 3 for a single packing run also shows pauses in the packing process, again in agreement with what was found in the stochastic rotation dynamic simulations in Ref. [1].

5. Conclusions

In conclusion, I have discussed the existing literature on computer simulations of DNA packaging and ejection inside and out of bacteriophage capsids. I have highlighted a number of quantitative issues which are still to a small or large extent open, in the physics of DNA packing and ejection in phage capsids. Most notably, it appears that modern simulations have more and more strongly suggested that the degree of nematic order is far from high inside a spherical capsid. I have also presented results obtained with a new Monte-Carlo algorithm on ϕ 29 packing which reinforce this suggestion.

Secondly, a quantitative separation between dynamical and thermodynamic contribution in the packing force and free energy loss upon packing in experiments and simulations has not been reached thus far. A way to realize this in practice might be to record several out-of-equilibrium force packing curves, extract the non-equilibrium work from these, and deduce from it the equilibrium (or thermodynamic) energy via the Jarzynski equality [15]. This possibility is at the moment under investigation. Another issue which this separation would finally clarify is the relative importance of entropy in packing force and free energy curves, with respect to the electrostatic and elastic contributions.

In general, simulations incorporating a realistic packaging dynamics are still quite rare and perhaps this hampers a quantitative comparison with the recent experiments, which have questioned the estimates of packing force and free energy losses of a large part of the theoretical literature. Finally, DNA ejection simulations are also in their infancy and more work will be required for instance to simulate ejection of long DNAs from phages, and to quantitatively compare on one hand with the predictions of existing scaling theories [12], and on the other hand with experimental data on ejection rates and times.

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I would expect these issues to prompt still longer and more realistic simulations in the next few years. I thank I. Ali and E. Orlandini for useful discussions.

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