A length-dynamic Tonks gas theory of histone isotherms

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We find exact solutions to a new one-dimensional (1D) interacting particle theory and apply the results to the adsorption and wrapping of polymers (such as DNA) around protein particles (such as histones). Each adsorbed protein is represented by a Tonks gas particle. The length of each particle is a degree of freedom that represents the degree of DNA wrapping around each histone. Thermodynamic quantities are computed as functions of wrapping energy, adsorbed histone density, and bulk histone concentration (or chemical potential); their experimental signatures are also discussed. Histone density is found to undergo a two-stage adsorption process as a function of chemical potential, while the mean coverage by high affinity proteins exhibits a maximum as a function of the chemical potential. However, fluctuations in the coverage are concurrently maximal. Histone-histone correlation functions are also computed and exhibit rich two length scale behavior.

Keywords: Tonks gas, protein-DNA binding, statistical mechanics

One-dimensional theories in statistical mechanics have been successfully applied to numerous biophysical systems, including DNA denaturation [1], particle transport across biological channels [2, 3], adsorption on 1D substrates [4, 5], and transport [6] along microtubules. In this Letter, we study protein-DNA binding and wrapping by solving a new 1D theory of interacting particles with dynamically varying particle sizes. DNA-histone protein complexes (nucleosomes) play vital roles in compacting DNA and regulating nucleic acid processing by mediating the accessibility by other regulatory proteins [7–9]. As shown in Fig. 1a, DNA can wrap around each histone protein complex at most 1.7 times (about 146 base pairs) [10, 11]. The base pairs that come into contact with each histone protein defines a footprint which we associate with particle lengths. We consider the collective behavior of the particles mediated only by the mutual exclusion of their footprints along a tensionless DNA substrate. We neglect the statistical mechanics of the linker DNA between the histone particles as well as the non-nearest-neighbor nucleosome-nucleosome interactions arising from their relative, three-dimensional conformations [12].

We now derive a generalization of the Tonks-Takahashi gas [13, 14] and apply it to DNA-histone interaction. Consider a 1D collection of \( N \) particles labeled by the positions \( x_i \) of their left-most edges and confined within length \( L \). The first particle is fixed at \( x_0 = 0 \). The minimum size \( a \) of each particle defines the infinite hard core repulsive interaction between adjacent particles such that \( |x_i - x_{i+1}| \geq a \) and \( N a \leq L \). Each particle \( i \) also carries an additional internal degree of freedom \( \ell_i \) which corresponds to its length. The length \( \ell_i \) may, as we shall see, describe the footprint of histone \( i \) on the DNA substrate (Fig. 1a). Since thermodynamic properties depend only on the interactions among particles, we compute the configurational partition function

\[
Z(N, L) = \int_0^{L_0} dy_{N-1} \cdots \int_0^{y_2} dy_1 \prod_{i=0}^{N-1} f(y_{i+1}, y_i),
\]

where \( y_i = x_i - ia \), \( y_N = L_0 = L - Na \), and

\[
f(y_{i+1}, y_i) = \int_0^{\ell_i^*} d\ell_i \exp \left[ -\int_0^{\ell_i^*} \varepsilon(x_i + \ell')d\ell' \right],
\]

where \( \ell_i^* = \ell_i^*(y_i, y_{i+1}) \) is the maximum possible wrapping around particle \( i \) and \( \varepsilon \) is a mesoscopic free energy for unit length extension. This winding-in energy consists of the molecular binding enthalpy to the histone particle, as well as local DNA bending and twisting energy. If we assume only non-sequence specific interactions and uniform extension energies (\( \varepsilon = \varepsilon_0 \), \( f(y_{i+1}, y_i) = f(y_{i+1} - y_i) \)). The integration limits in (1) reflect the particles’ impenetrability and renders \( Z(N, L) \) convolutions of the functions \( f(y_{i+1} - y_i) \). Upon using Laplace transforms in the variable \( L_0 \),

![FIG. 1: (a) A histone-covered segment of DNA. DNA can partially wrap nucleosome particles depending on solution ionic strength [11, 15]. (b) The 1D representation of the footprint of the histone-wrapped regions of DNA (thick sections). The associated particle lengths can vary from \( a \) to \( a + w \).](image-url)
\[
Z(N, L) = \int_{\gamma-i\infty}^{\gamma+i\infty} \hat{f}^N(s)e^{sL_0} \frac{ds}{2\pi i},
\]

where \( \hat{f}(s) \) is the Laplace transform of \( f \) and \( \gamma \in \mathbb{R} \) is greater than the real parts of all singularities of the integrand. From (3), one readily finds thermodynamic quantities such as moments of the particle lengths \( \ell_i \),

\[
\langle \ell_i^n \rangle = \frac{(-1)^n}{Z} \oint \hat{f}^{N-1}(s) \frac{\partial^n \hat{f}(s)}{\partial \varepsilon_0^n} e^{sL_0} \frac{ds}{2\pi i},
\]

positions \( \langle y_i^n \rangle \), and particle separations \( \langle (y_{i+1} - y_i)^n \rangle \).

Although these quantities are readily computed using specific functions \( f(s) \), the resulting sums typically involve numerical manipulation of extremely large numbers, especially for large \( N \). Thus, it is also useful to derive from (3), using steepest descents, the leading order large \( N \) asymptotic approximation \( Z(N \to \infty, N/L = \rho) \sim e^{N(s^1/\rho - a) + \gamma f(s^*)} \), where \( s^* \) is the saddle point defined by largest root of

\[
\frac{1}{f(s^*)} \frac{\partial f(s)}{\partial s} \bigg|_{s=s^*} + \left( \frac{1}{\rho} - a \right) = 0.
\]

Thermodynamic limits of, for example, the moments of the mean particle lengths (4) become

\[
\langle \ell_i^n \rangle \sim \frac{(-1)^n}{f(s)} \frac{\partial^n f(s)}{\partial \varepsilon_0^n} \bigg|_{s=s^*}.
\]

In the histone winding problem (Fig. 1) the unit of length will be a single nucleic acid base pair (bp). The total length \( \ell_i \) of each particle corresponds to the arc-length of polymer that is wrapped around, and in direct contact with, a histone particle. The hard core cut-off \( a \) depends on details of the three-dimensional arrangement of adjacent histones, and is roughly (or slightly smaller than) the diameter of a histone particle. Only for very specific phased orientations of canted histones along DNA can the histones be spaced less than about \( a \approx 20 \text{bp} \) \([7, 10–12]\). The finite width of the histone limits “winding-in” lengths \( \ell_i \) to either the distance to the start of an adjacent particle, \( x_{i+1} - x_i - a = y_{i+1} - y_i \), or to \( w \approx 146 \text{bp} \), the maximum winding length corresponding to 1.7 loops around a histone particle. For example, particles zero and one in Fig. 1a have only one base pair of contact (\( \ell_0 = \ell_1 = 0 \)), particles two and three are fully wound in \( (\ell_2 = \ell_3 \approx 146) \), while particle four is partially wound in \( (0 < \ell_4 < w) \). Upon imposing the physical limits on the particle lengths,

\[
\ell_i^* = \begin{cases} 
  x_{i+1} - x_i - a & x_{i+1} - x_i - a < w \\
  w & x_{i+1} - x_i - a > w,
\end{cases}
\]

in the integration limit in (2), we find

\[
\hat{f}(s) = \frac{1 - e^{-(s + \varepsilon_0)w}}{s(s + \varepsilon_0)}.
\]

With this form of \( \hat{f}(s) \), the integrand in (3) appears to have a pole at \( s = 0 \); however, an implicit constraint on the number of particles of total length \( a + \ell \) that can fit into \( L \) will “induce” poles at \( s = -\varepsilon_0 \). This is seen by expanding \( \hat{f}^N(s) \) in the integrand of (3),

\[
Z(N, L) = \sum_{k=0}^{N} \int_{\gamma-i\infty}^{\gamma+i\infty} e^{-k\varepsilon_0 w} e^{s(La - kw)} \frac{ds}{2\pi i},
\]

where \( a_k \equiv (-1)^k \binom{N}{k} \). For \( \gamma > \max\{0, -\varepsilon_0\} \) and \( (L - Na - kw) > 0 \), we close the contour in the left-hand \( s \)-plane. For \( L \) and \( k \) such that \( (L - Na - kw) < 0 \), convergence demands that we close the contour in the right \( s \)-half-plane. Since there are no poles to the right of \( \gamma \), terms with \( (L - Na - kw) < 0 \) correspond to configurations with more particles in \( L \) than is possible, and do not contribute to the partition function. Therefore, we need only sum (9) to \( k = k^* = \min\{ \lfloor (L - Na)/w \rfloor, N \} \). Expanding all terms and explicitly evaluating the residues at \( s = 0, -\varepsilon_0 \), we obtain the exact expression,

\[
Z(N \geq 1, L) = \frac{(-1)^N N!}{\Lambda^{N-1} \sum_{k=0}^{N} a_k b_p (L - Na - kw)^p} \times \prod_{k=0}^{p} \left[ e^{-\varepsilon_0 (L - Na)} - (-1)^p e^{-k\varepsilon_0 w} \right],
\]

Fig. 2a plots the saddle solution \( s^* \) found from (5). In the fixed \( N \) ensemble, the probability distribution for particle \( i + 1 \) to be at position \( x_{i+1} \) given that particle \( i \) is at position \( x_i \) is readily computed in the asymptotic limit \( (L \gg N \gg a) \). \( \frac{\partial^2}{\partial x_{i+1} \partial x_i} Z(N, L-x)/\int_0^L Z(N, L-x)dx = s^*e^{-s^*(s-a)} \). This result implies that the adjacent particle is statistically confined to within \( x \lesssim 1/s^* \) \([16]\). At low number densities, adjacent histones are spaced far apart and \( s^* \sim \rho/(1 - \rho a) \). For attractive lengthening interactions \( (\varepsilon_0 \ll 0) \), a sharp increase in \( s^* \) occurs near \( \rho \sim 1/(w + a) \) signaling a partial confinement of hard rod particles of roughly size \( w + a \). At extremely high densities, \( \rho \sim a^{-1} \), particles are compressed at the expense of unwinding, and \( s^* \) increases further as \( s^* \sim 2\rho/(1 - \rho a) - \varepsilon_0/2 \). Fig. 2b shows the mean winding-in length (normalized by \( w \)), found from (6). At low densities and strong attractive binding, the maximal winding in length \( w^{-1}(\ell) \sim 1 \) is approached, while at high densities, the winding-in length is restricted by nearest neighbors and \( (\ell) \approx 1/\rho \).
can fit into length; we find $\epsilon \equiv (3)$ or $(10)$ in $\Xi$\n\n...tones at intervals of the linker length $a$ which can be evaluated using $(8)$ to yield $\Xi$\n\nFIG. 2: Thermodynamic properties for $a = 20, w = 146$, and various $\varepsilon_0$. (a) The root $s^*$ of $(5)$ that defines $Z(N \to \infty, N/L = \rho)$ and determines the next-neighbor correlation function $g^{(2)}(x_{i+1} - x_i|N) = s^* e^{-s^*(\varepsilon_0)}$. (b) Winding-in lengths $w^{-1}(\mu)$ as a function reduced density $\rho w$. (c) Number density as a function of chemical potential $\mu$ for various binding affinities $\varepsilon w$. An intermediate density plateau at $(\rho) \approx a/(w + a)$ for high affinity histones due to close packing of fully wound-in particles of length $w + a$. (d) Mean coverage as a function of $\mu$. Curves correspond to the legend used in (b). Maxima arise for wound-in, high affinity particles spaced an average distance $w + a$ apart. The high compression $(\mu \to \infty)$ limit forces unwinding but packs histones at intervals of the linker length $a$ for a coverage fraction $(\theta) \approx 1/a$.

Histone-DNA affinity and competition experiments however, are performed by exposing DNA to fixed bulk histone concentrations [11, 17]. When the mean bound histone number is determined by the bulk histone chemical potential (thus not necessarily large), we employ the grand partition function found using the exact expression $(3)$ or $(10)$ in $\Xi(\lambda, L) \equiv \sum_{N=1}^{N^*} \lambda^N Z(N, L)$. The fugacity $\lambda \equiv e^{\mu - \varepsilon_0}$ takes into account the bulk histone chemical potential, and the binding energy $\varepsilon_0$ of a single base pair. $N^* = \text{int}(L/a)$ is the maximum number of particles that can fit into length $L$. In the $L/a = \infty, N^* = \infty$ limit, we find

$$\Xi(\lambda, L \to \infty) = \oint \frac{\lambda e^{-s \alpha} f(s) e^{\alpha L}}{1 - \lambda e^{-s \alpha} f(s)} \frac{ds}{2\pi i},$$

which can be evaluated using $(8)$ to yield $\Xi(\lambda, L \to \infty) = \langle \rho \rangle e^{\alpha L}$, where the mean density $\langle \rho \rangle \equiv L^{-1} \partial_\lambda \ln \Xi$ is explicitly

$$\langle \rho \rangle = \frac{s_+(s_+ + \varepsilon_0)}{2s_+ + \varepsilon_0 + \lambda e^{-s_*}(a - (w + a)e^{-(s_+ + \varepsilon_0)w})},$$

$s_+$ being the largest real root of $1 - \lambda \hat{f}(s_+) e^{-s_* a} = 0$. The mean fraction of DNA base pairs covered by contacts with histones is then found from

$$\langle \theta \rangle = \frac{-1}{L} \frac{\partial \ln \Xi}{\partial \varepsilon_0} + \langle \rho \rangle.$$  

The mean density and coverage are plotted in Figs. 2c,d. For $\mu \to -\infty$, $\langle \rho \rangle \sim s_+ \sim e^{-\varepsilon_0 + \mu}(1 - e^{-\varepsilon_0 w})/\varepsilon_0 \to 0$ since this limit corresponds to infinitely dilute bulk histone concentration. Densities of adsorbed particles increase with bulk histone chemical potential. For higher affinity histones, these increases occur earlier and plateau at a value corresponding to close packing of fully wound-in particles, or $\langle \rho \rangle a \approx (w + a) \approx 0.12$. As $\mu$ and the density further increase, particles compress and unwind each other until the density approaches maximal packing at $\langle \rho(\mu \to \infty) \rangle \sim 1/a - 2/(\mu a) + O(\mu^{-2} \ln \mu)$. This crossover behavior is seen only for high affinity ($\varepsilon_0 < 0$) histones. The transition from monotonic to the two-stage density behavior may be observable by tuning the non-specific histone binding energies $\varepsilon_0$ by e.g. varying ionic strength [11, 15].

DNA accessibility (and hence occlusion by histone particles) and positioning is thought to be a major determinant of nucleic acid processing by other regulatory proteins [7–9, 11]. The total coverage $\langle \theta \rangle$ defined as the mean fraction of base pairs in contact with histones, is shown in Fig. 2d. For $\mu \to -\infty$, there are few particles present to adsorb onto the DNA substrate and $\langle \theta \rangle \sim e^{-\varepsilon_0 + \mu} \to 0$. An increase in mean coverage results from increasing $\mu$ and the number of bound histones. The theoretical maximum coverage $w/(w + a) \approx 0.88$ (thin dashed line) corresponds to close packing of fully wound-in particles and is approached only for high affinity histones. The minimum uncovered fraction $a/(w + a)$ results from the linker DNA of minimum length $a \sim 20$ joining two adjacent nucleosomes. If $\mu$ is further increased, the particles squeeze on each other until they unwrap to the point where only a single base pair remains in contact for each histone. In this limit, the mean coverage $\langle \theta(\mu \to \infty) \rangle \sim 1/a + (1 - 2/a)/\mu + O(\mu^{-2} \ln \mu) \approx 0.05$ while the histones are spaced at their maximal densities $\langle \rho \rangle \approx 1/a$. The variance in coverage, $\text{var}(\theta) = L^{-1} \partial^2 L^{-1} \partial_\varepsilon \Xi / \partial \varepsilon_0 + \Xi / \partial \varepsilon_0$, gives a standard deviation in coverage proportional to the mean coverage, $\sqrt{\text{var}(\theta)} = \sqrt{\text{cov}(\theta)}$. Despite the high coverage at intermediate chemical potentials, fluctuations in this regime are also maximal, suggesting a dynamically controlled DNA accessibility mediated by histone-histone interactions.

In the grand ensemble, the correlation function analogous to $g^{(2)}(x_{i+1} - x_i|N) = \langle \rho \rangle g^{(2)}(x|\mu) \equiv \Xi(\lambda, x)\Xi(\lambda, L - x)/\Xi(\lambda, L)$ which describes the probability distribution
that given a particle at the origin, any other histone exists at $x$. When $x \gg 1/\langle \rho \rangle$ and $N^* < \infty$, the exact expression (10) must be used to compute $\Xi(\lambda, x)$. Fig. 3 shows $g^{(2)}(x|\mu)$ computed for various values of $\varepsilon_0, \mu$. Finite particle size anticorrelations give rise to oscillations at two length scales (see Fig. 3 caption) depending on finite particle size anticorrelations give rise to oscillations at two length scales (see Fig. 3 caption) depending on affinity $\varepsilon_0$ and density $\langle \rho(\mu) \rangle$.

![Fig. 3: The correlation $g^{(2)}(x|\mu)$ exhibits properties of both length scales $a$ and $w$ depending on $\varepsilon_0$ and $\mu$. For high affinity and low densities (e.g., $\varepsilon_0w = -30, \mu = -5$), the density distribution is similar to that of a hard rod Tonks gas of length $a + w$. Upon increasing the density ($\varepsilon_0w = -30, \mu = -2$), features associated with both length scales arise as partial unwinding occurs, exposing the hard core repulsion of size $a$. Conditions under which particles weakly wind in ($\varepsilon_0w = -10$) exhibit behavior attributed to hard rods of length $a$. However, even at lower affinities ($\varepsilon_0w = -8$), behavior approximating that of rods of length $w + a$ can be recovered if densities are made sufficiently low ($\mu = -15$).](image)

The proposed model considers only the adjacent histone exclusion interactions mediated by nonoverlapping footprints and neglects sequence specific and nucleosome-nucleosome interactions arising in compact, 3D chromatin structure. Nonetheless, our theory can be solved exactly with uniform wrapping energies $\varepsilon_0$ to give reasonable results for winding-in lengths ($\ell$) and histone-histone correlations $g^{(2)}(x|N)$ and $g^{(2)}(x|\mu)$. The model predicts a two-state adsorption process and a maximum in the DNA coverage fraction $\langle \theta \rangle$ as a function of bulk histone concentration and binding affinity. However, fluctuations in the coverage are also concurrently maximal during the peak in mean coverage, indicating that thermal effects can nonetheless provide dynamic access to highly covered DNA. These predictions can be tested experimentally by varying bulk histone coverage and ionic strength (although this would also affect DNA bendability and $\varepsilon_0$) [11, 15], provided short enough DNA segments are used such that large scale 3D structures do not arise and non-nearest-neighbor interactions remain irrelevant.

The model can be readily generalized to include the effects of linker DNA twist, externally applied tension [18], and relative histone orientation [12] on the cut-off $a$. Specific sequences, and their effects on local bendability, twistability, and histone affinity has also been found to be important in vitro [11] and can be treated within a similar framework, although completely generalizing our model to include specific sequences [11, 17] (spatial dependence of $\varepsilon(x)$), would require computational approaches.

Finally, we can extend the Tonks-Takahashi model by removing the maximal winding length constraint ($w \to \infty$). The resulting model can then be applied to problems of 1D nucleation and polymerization. Particles would correspond to a nucleation domains that cannot coalesce due to perhaps growth asymmetry (as in actin filaments) or incommensurability with the underlying substrate [5, 19]. The “winding-in” or polymerization length $\ell$ is now the degree of polymerization in that domain. Since $\ell_i$ are limited only by the position of adjacent domains, $\ell_i^* = x_i + 1 - x_i - a$ and $\ell_f(s) = [s(s + \varepsilon_0)]^{-1}$. Results analogous to those obtained for the histone problem are found by setting $w = \infty$ in (12-13). The qualitative behavior of $\ell(\varepsilon_0)$ can be found in closed form in the $N = \infty, a = 0$ limit: $\rho^u(\ell_i^*) \sim 2^n n!/(z + 2 + \sqrt{z^2 + 4})^n$, where $z \equiv \varepsilon_0(1 - \rho a)/\rho$. This result also implies $\langle \ell_f^2 \rangle = \langle \ell_i^2 \rangle^2$. The behaviors for $w = \infty$ are qualitatively different from those shown in Fig. 2. Namely, the adsorption isotherm is monotonic and the coverage has a minimum at intermediate $\mu$ when $\varepsilon_0 < 0$ and vanishes for $\mu = -\infty$ if $\varepsilon_0 > 0$. Such differences highlight the importance of the additional length scale $w$ unique to histone binding.

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