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Condensation of DNA and RNA in solution

1. **Collapse of a single polymer chain: Effect of chain stiffness and attraction range**
   Authors: Yanyan Zhu, Haim Diamant, and David Andelman
   arXiv:2601.09908

2. **Long ssRNA undergoes continuous compactification in the presente of polyvalent cations**
   Authors: Ana Luisa Duran-Meza, Liya Oser, Richard Sportsman, Martin Phillips, Charles M. Knobler, and William M. Gelbart
   Biophysical Journal 122, 3469-3475, 2023

Recommended with a Commentary by Achille Giacometti
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Double-stranded DNA (dsDNA) is a highly charged polyelectrolyte with a significant bending rigidity (the persistence length l_p is of the order of 50 nm), which acquires a highly extended conformation in pure water. However, it collapses in the presence of multivalent cations, thus explaining the tight packing of DNA observed in capsids and inside cells. *In vitro* experiments have provided evidence of the possible conformational topologies of dsDNA condensates, in the form of nematic bundles or toroidal spools [1], and of the fact that this condensation process is discontinuous, akin to a first-order transition in the limit of an infinitely long number of nucleotides.

While this phenomenon has been studied in detail and is now well understood, much less attention has been devoted to the counterpart collapse properties of long single-stranded RNA (ssRNA). For this reason, a recent study by Knobler, Gelbart and collaborators, which is the second subject of the present comment, is particularly welcome, as it addresses exactly this problem using dynamic light scattering, analytical ultracentrifugation, and gel electrophoresis, for five different ssRNA molecules ranging in length from 3234 to 11 703 nucleotides. As a benchmark, the authors also studied, with the same methods, the condensation properties of a 48.5 kbp-long dsDNA. From dynamic light scattering it is possible to measure the hydrodynamic diameter, which is proportional to the radius of gyration and can then be monitored as a function of cation concentration. While in the case of dsDNA they clearly observed a bimodal distribution of condensate sizes, suggesting a discontinuous transition in line with the common view, a unimodal distribution was instead observed for ssRNA, suggesting a continuous transition (second order, in the language of critical phenomena).

A key difference between the two biopolymers is clearly the bending rigidity, as ssRNA is believed to be a highly flexible polyelectrolyte, albeit dependent on counterion concentration. This could lead to a simple theoretical explanation, as it is well known that a flexible polymer undergoes a continuous coil–globule transition. However, there is another length scale in the problem, namely the range of effective attraction r_c between different monomers mediated by the solvent. Hence, one could expect that what matters is the ratio l_p/r_c between the persistence length and the range of effective attraction. The first subject of this comment , which is the recent paper by Zhu et al, makes precisely this point.

The literature on theoretical studies of the coil–globule transition of polymers in solution is abundant, starting from classic works by Lifshitz, de Gennes, Grosberg and many others, and leading to the first experimental observation, again using dynamic light scattering [2]. A modern view started with the seminal work by Doniach, Garel and Orland [3], who mapped a self-avoiding walk with an energy penalty at each turn onto an n-vector model whose phase diagram can be studied within a mean-field approximation. In the temperature–bending rigidity plane, they found a double transition (second order followed by first order) upon cooling up to a critical value of the bending rigidity, and a single first-order transition above this value. This prediction was quickly verified numerically, first on lattice [4, 5] and then extensively off lattice (see the recent work in Ref. [6] and references therein). A key observation of the work by Zhu et al. is that the persistence length l_p is increased either by increasing the bending rigidity or by lowering the temperature. This should be contrasted with the only other length scale in the problem, namely the range r_c of the attractive interaction, which is usually set to nearest neighbors to reflect the short-range nature of this effective interaction. However, we know that the actual value of r_c critically affects the phase behavior: as r_c increases, more and more monomers fall within the attraction range, thus favoring the globular phase. Zhu et al. extended the range r_c of the on-lattice simulations by Bastolla and Grassberger [4] and compared it with the persistence length l_p They found a discontinuous collapse for $l_p > r_c$, in agreement with past work and with experiments on dsDNA condensation, and a continuous collapse in the opposite limit $l_p < r_c$, in agreement with the experiments on ssRNA condensation by Gelbart and collaborators. Essentially, the two-dimensional temperature–bending rigidity plane collapses onto a single line l_p/r_c when using l_p instead of the bending rigidity.

It is important to recall that the theta temperature T_θ separating the coil from the globule regime is a single temperature only in the limit of an infinitely long polymer. For finite polymer length, it is a region whose width decays as $1/N^{1/2}$ [7]. Care must therefore be exercised in obtaining this value numerically, but how does it depend on polymer stiffness? As stiffness increases, the entropy decreases (fewer possible conformations), whereas the energy increases both because of the increasing stiffness and because of the decrease in the number of favorable contacts. This would suggest an increase in the transition temperature in contrast with naive expectation but in agreement with both mean-field theory [3, 8] and numerical simulations [4, 5, 6]. Zhu et al. shed some light on this point by considering the ratio T_θ/r_c^3, where r_c^3 represents a measure of the attractive energy, as a function of the persistence length l_p, thus allowing a comparison across different values of l_p/r_c. Again, they found that the curve can be positively, zero, or negatively sloped depending on the value of r_c, thereby reconciling previous contradictory results.

A concrete mechanism relating the range of the monomer–monomer attraction to the rounding of the critical collapse transition can be inferred from the classic de Gennes blob picture. In the usual framework, the transition emerges as a balance between short-range attraction and steric repulsion, thus leading to a discontinuous collapse. If the attraction is weak but long-ranged, it will dominate at long distances, whereas steric repulsion dominates at short distances. Zhu et al. argue that this leads to a completely different scenario in which gradual contraction is a natural consequence.

Overall, the combination of these two studies paves the way to several additional questions that would be interesting to pursue. Single-stranded DNA molecules are also very flexible, and they usually bind to complementary partners in a crowded environment. How would they behave under infinite-dilution conditions, as in the experiments of Duran-Meza *et al*? At the same time, the current coarse-grained description by Zhu *et al.* does not distinguish between the two cases, but it is nowadays possible to perform atomistic simulations that do. It would be interesting to address both these questions.

References

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