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Order through entropy

Daan Frenkel

Understanding entropic contributions to common ordering transitions is essential for the design of self-assembling systems with addressable complexity.

Irreversible changes in physical systems — such as the breaking of a glass on hitting the floor or the formation of a crystal from its melt — only occur because of an increase in entropy (Box 1). Yet the formation of a crystal seems to be at odds with the widespread notion of entropy as a measure of disorder. If, under the same conditions, a crystal does indeed have lower entropy than the melt from which it forms, does this mean that crystallization cannot happen? The answer is, of course, that crystallization can occur because the system is in contact with the environment: on freezing, the heat released increases the entropy of the surroundings by an amount that is larger than the entropy decrease incurred in the transition from liquid to crystal.

However, the situation becomes more interesting when considering systems that cannot release heat to 'pay' for a local decrease in entropy. Hard (colloidal) particles — that is, particles that cannot overlap with each other and for which the internal energy does not depend on particle arrangement — are an example. Can such athermal systems order spontaneously? This would only be possible if the entropy of the ordered phase were higher than that of the disordered phase at the same density and temperature. Clearly, such an ordering transition would not be possible if entropy were a measure of visible disorder. However, over the past decades many examples have emerged where athermal systems do undergo transitions that increase both visible order and entropy.

Entropic ordering

To my knowledge, the earliest example of a system that has an ordered phase with higher entropy than that of the disordered phase at the same density is Lars Onsager's model for a fluid of

Box 1 | A brief explanation of entropy.

Just as in biology 'nothing makes sense except in the light of evolution'[18], the spontaneous changes that take place in macroscopic physicochemical systems cannot be understood except in the light of the second law of thermodynamics. The second law emerged from the simple, empirical observation that heat does not spontaneously flow from a cooler to a hotter body. Rudolf Clausius showed that this observation implies that there is a quantity — which he called entropy and defined in a sentence spanning 14 lines — that always increases during irreversible changes in isolated systems[19]. In the final sentence of his 1865 paper, Clausius summarized the implications of his momentous finding by stating that the entropy of the Universe tends to a maximum. Few laws in physics seem to be based on stronger evidence than the second law.

Clausius gave no microscopic interpretation of entropy. It was instead Ludwig Boltzmann, Willard Gibbs and Max Planck who established the relation between entropy and the atomistic description of nature. This relation is captured by the equation $S = k_B \ln W$, which is chiselled into Boltzmann's gravestone (even though Boltzmann never wrote 'his' equation in this form; Planck was the first to do so[20,21]). The equation states that the entropy, S, is equal to the logarithm of the number of states accessible to the system, W, multiplied by a constant (Boltzmann's constant, k_B).

The second law then implies that an irreversible change in a closed system is only possible if the number of states that correspond to the final state is (much) larger than that of the initial state. In classical statistical mechanics, the 'number of states' gets replaced by the accessible volume in phase-space, but the basic statement of the second law remains the same: systems do not move spontaneously from a large volume in phase space to a (much) smaller one. The word 'much', however, requires a comment. When the entropy of a system is increased by only one joule per kelvin (a change of less than 0.1% for one litre of ambient water), then the number of accessible states increases by the staggering factor $10^{10^{22.5}}$, a number so large that it cannot be captured by any analogy that makes sense.

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thin, hard rods[1]. Onsager's work returns time and again when considering phase transitions where ordering is associated with an increase in entropy: in every case, there are several contributions to the entropy — in Onsager's case, the entropy associated with the translational and orientational degrees of freedom of the rods — and ordering takes place because at the transition one contribution is larger than the other.

In fact, Onsager's theory describes the transition from an isotropic (orientationally disordered) fluid phase to a nematic (orientationally ordered) phase of thin, hard rods. In the nematic phase, the rods are, on average, aligned parallel to each other, but not perfectly so: there is a spread in their orientations around the average alignment direction. To understand orientational entropy, one can assume that the number of possible orientations of the rods is a large but finite number, M. Then a fluid of hard rods can be viewed as a mixture of M different components. If the probability P_i to find a rod in any of its M orientations in the fluid is identical for $i = 1, 2, \ldots, M$ (which means that the probability, per unit solid angle, to find a given orientation is independent of

direction) then the orientational entropy can be written as

$$S(\text{isotropic}) = -k_B \sum_{i=1}^{M} P_i \ln P_i =$$
$$-k_B \sum_{i=1}^{M} \frac{1}{M} \ln \frac{1}{M} = k_B \ln M$$

However, if the rods are aligned, the probabilities P_i are not all the same, and hence

$$S(\text{nematic}) = -k_B \sum_{i=1}^{M} P_i \ln P_i \leq S(\text{isotropic})$$

Clearly, for hard rods orientational ordering decreases orientational entropy (the correct definition of the orientational entropy would include a term that depends on the discretization but that is irrelevant to the difference $S(\text{nematic}) - S(\text{isotropic})$). However — and this is the crux of Onsager's argument — orientational ordering increases translational entropy. To see this, one can compare the excluded volumes for two rods with diameter D and length L when constrained to be either parallel or perpendicular to each other (Fig. 1a). As the ratio of excluded volumes for the parallel and perpendicular scales as D/L, in the

limit of very thin, very long rods — that is, when $D/L \to 0$ — the excluded volume for parallel rods becomes negligible. Therefore, a fluid of thin and long aligned rods behaves as an ideal gas, with an entropy per rod (for N rods in volume V) equal to $k_B \ln(V/N)$, which is a well-known result of statistical mechanics (as before, terms that are unaffected by the phase transition can be ignored). However, for N orientationally disordered rods, a given rod is excluded from a volume of the order of $O(NL^2D)$. The larger the excluded volume (or the smaller the accessible volume), the lower the translational entropy. Therefore, orientationally disordered rods can increase translational entropy by becoming more aligned — that is, at the expense of some orientational entropy. In fact, Onsager showed (see ref. 2 for a review) that translational entropy can be gained at the expense of orientational entropy only beyond a certain density.

This hand-waving discussion of Onsager's theory of the isotropic–nematic transition illustrates the key aspects of all ordering phase transitions (or for that matter, other local ordering phenomena) that are accompanied by an increase in entropy: in every single case, one type of entropy decreases and another kind of entropy increases such that the total entropy becomes larger. In other words, entropy-driven ordering is not a violation of the second law.

Another common example of entropy-driven ordering is that of the freezing of hard spheres. The first indications that a fluid of hard spheres might freeze came from numerical simulations carried out by William Wood and J. D. Jacobson[3] and by Berni Alder and Thomas Wainwright[4]. As the formation of an ordered crystal from a disordered liquid seems to be the epitome of an ordering transition, the simulations were received with much scepticism, to the extent that at a workshop in 1957[5] a panel of experts (including two Nobel laureates) were asked to vote whether they believed in the evidence for hard-sphere freezing. It was a draw; the Chair (George Uhlenbeck) then tipped the balance by voting against. Since 1957, the situation has changed drastically: not only is hard-sphere freezing now widely accepted, but there exist many theories and, more importantly, experiments[6] that provide direct evidence for the existence of a transition where hard spherical particles spontaneously freeze. What entropy trade-off makes such freezing possible? Again, it is useful to relate the entropy per particle to the logarithm of the volume accessible to that particle. For a crystalline solid, the accessible volume can be simply and

intuitively interpreted as the space within which a particle can move without bumping into the particles sitting on adjacent lattice sites. If the crystal is densely packed, such free volume tends to zero (Johannes Kepler demonstrated that this happens when the spheres occupy a fraction $\pi/\sqrt{18}$, or about 74%, of the total volume). In the dilute fluid phase, free volume per particle is much larger (for an ideal gas it is V/N). However, as the density of the fluid is increased, free volume per particle decreases rapidly and reaches zero at the so-called random-close-packing point, which occurs at a volume fraction of about 64%. Hence, at higher densities, hard spheres must crystallize (at least in part) to gain accessible volume and thus entropy. Yet crystals are not the only ordered structures that can form on compression of a hard-sphere fluid; hard colloids can also form highly ordered icosahedral clusters that are less dense than the Kepler packing yet certainly denser than any fluid[7].

Since the early work of Onsager, Wood and Alder, entropic ordering transitions have been found to be extremely common, certainly in colloidal matter. Simulations have shown that entropic effects alone can account for a wide variety of lyotropic liquid-crystalline phases that have been observed in experiments[8]. More recently, simulations on a wide range of convex, hard polyhedral particles have demonstrated that entropy can drive the formation of a whole zoo of crystals, liquid crystals, and even quasicrystals[9].

But there are even simpler examples of phenomena where entropy plays a counterintuitive role. For example, in the mixing of colloidal particles and smaller globular polymers, the colloids and the polymers separate into two fluid phases, one containing mainly colloids, the other containing mainly polymers[10]. And this happens in the absence of attractive forces between the colloids or the polymers. The simplest description of the physics underlying this demixing phenomenon was given some 50 years ago by Sho Asakura and Fumio Oosawa[11], who showed that the purely repulsive interaction between the polymers and the colloids can induce an effective attractive interaction between the colloids (the implications of this so-called depletion interaction for colloidal demixing were first explored in 1976[12]). The Asakura–Oosawa model assumes that the polymers only interact with the colloids (that is, that the translational entropy of a pure polymer solution is that of an ideal gas), and that the polymers behave as spherical particles with radius R_P and are completely excluded from a shell with radius $R = R_P + R_C$ around

the centre of each colloid with radius R_C. Rather than to work out the consequence of this model in detail (for this, see ref. 13, for example), one can consider a one-dimensional case: a mixture of colloidal rectangles and polymer disks, alternately positioned along a line (Fig. 1b). If the length available to such a mixture is shorter than the sum of the diameters of all colloid and polymer particles, the system is jammed (that is, there is absence of translational freedom). However, when the polymers and the colloids are separated, they easily fit within a length larger than the sum of the diameters of the colloids alone. This explanation, albeit simplistic, clearly illustrates that under certain conditions mixtures of hard particles can increase their entropy by demixing. The story becomes more

complicated if the polymers can adsorb on the colloids[14], however.

The recurring theme in all the above examples is that virtually all phase transitions involving liquids, vapours, crystals or liquid crystals, even those transitions whose occurrence is commonly attributed to attractive energetic interactions, can be reproduced by using entropy alone. This is important because in experiments entropic interactions can be tuned: colloidal particles with a variety of shapes can be synthesized, and the size and concentration of the polymers (or other smaller colloidal particles) that cause the depletion interaction between the colloidal particles can be controlled. We thus have far greater control over the interactions between colloids than over those between small molecules. This is of crucial
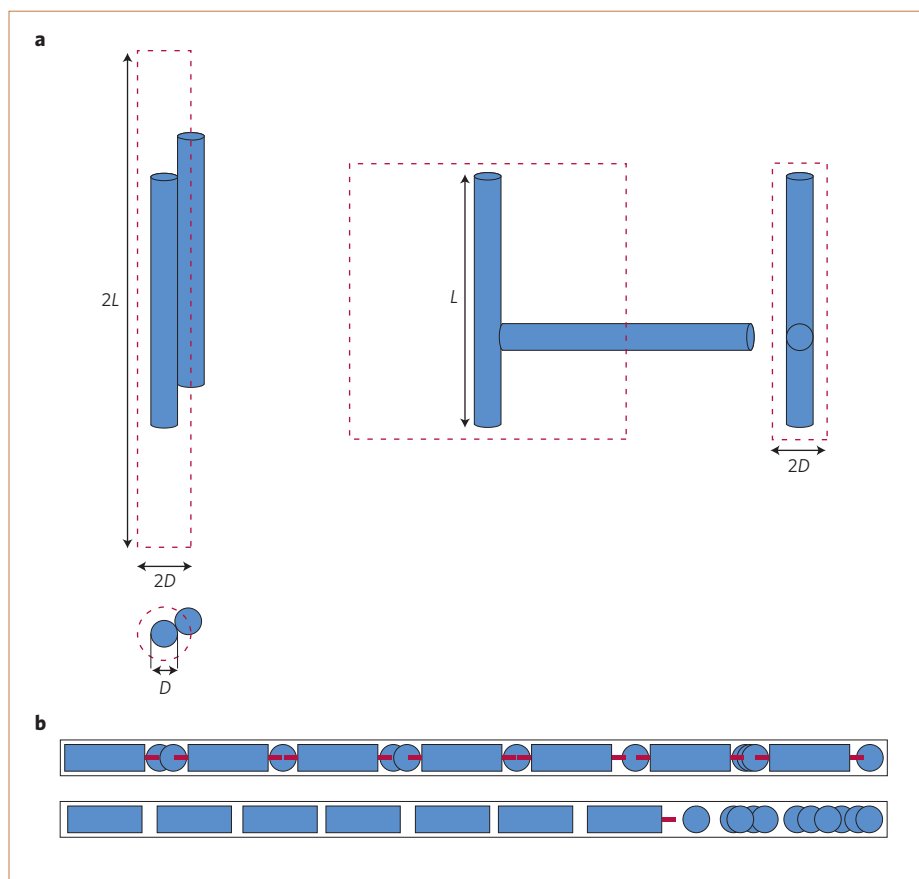
Figure 1 | Entropic forces. a, A rod with length L and diameter D excludes the geometrical centre of a second identical rod from occupying a certain volume (red lines). In the limit of $L \gg D$, this volume is minimal ($2\pi L D^2$) if the rods are parallel and maximal ($2L^2 D$) when they are perpendicular. Hence, rod alignment maximizes translational entropy (and above a certain density, the gain in translational entropy outweighs the loss in orientational entropy). **b**, Simplified, one-dimensional example of the depletion interaction. The blue rectangles cannot overlap with each other or with the disks (that is, the centres of the disks are 'depleted' from the regions shown in red), but the disks can intersect. In this system, a configuration of alternating rectangles and disks (top) has less entropy than a system where the rectangles and disks are separated (bottom), because in the latter the particles have more freedom of motion (the total area accessible to the disks is larger).

Figure 2 | Schematic of the self-assembly of 'DNA bricks' (each of which is a 32-base string of single-stranded DNA that can bind to four neighbouring bricks) into a complex structure where every brick is distinct and has a unique position. Figure reproduced with permission from ref. 15, © 2012 American Association for the Advancement of Science.

importance for the design of complex self-assembling structures.

Addressable complexity

Crystals, liquid crystals and quasicrystals can all form by self-assembly of tailor-made colloidal building blocks, and these can be designed so that such ordered structures increase the entropy of the system. Indeed, over the past few decades much of the research on complex self-assembly has focused on materials with structural complexity. Yet there is another form of complexity that needs to be mastered if we are ever to make complex self-assembled machines or devices consisting of many distinct building blocks, each of them located in a pre-specified position. Such 'addressable complexity' is different from that in a one-component crystal, where permutations of the building blocks do not affect the properties of the material. Instead, systems with addressable complexity can in principle self-assemble from hundreds or even thousands of distinct components, as exemplified by the self-assembly of short single-stranded

'DNA bricks' into complex finite structures in which every DNA brick occupies a predetermined position[15] (Fig. 2). Of course, the self-assembled DNA structure contains much more information than a one-component crystal. For example, there is only one way in which a structure consisting of N bricks can be assembled correctly. In contrast, in a crystal of N identical colloids there are $N!$ ways to distribute the colloids over the crystal without changing its properties. Hence, to make the DNA structure addressable, the entropic cost of the encoded information, described by the entropy per particle $s_{address} = k_B(\ln N - 1)$ assuming that $N \gg 1$, has to be 'paid' during self-assembly. Indeed, the free energy of DNA hybridization compensates for the high entropic cost of addressable self-assembly. In principle, purely entropic 'lock–key' interactions — depletion attractions between pairs of colloids of appropriately designed shape — might achieve the same (but the design of the building blocks would be nontrivial). However, because the entropic cost per (colloidal) particle (or brick) increases with N, ever-stronger specific pair interactions are needed to make increasingly larger structures with addressable complexity. Also, in these structures, nonspecific interactions between particles that should not be adjacent in the target structure should be sufficiently weak so as to be easily broken during the self-assembly process — that is, the structure must be able to anneal. The problem is that the stronger specific interactions needed to overcome the entropic cost involved in the design of larger structures almost inevitably imply the presence of stronger nonspecific interactions. If the latter become significantly larger than the thermal energy at the assembly temperature, the kinetics of self-assembly are compromised[16]. The existence of such a kinetic barrier does not necessarily mean that the design of large structures with addressable complexity is doomed. Rather, it suggests that assembly will have to follow a protocol where not all units assemble at the same time. Possible hierarchical assembly scenarios are discussed elsewhere[17]. At present, experiments to assemble complex addressable structures exploit the selective binding properties of complementary DNA strands, yet other 'ligand–receptor' pairs

might be used in future provided that they exhibit similar selectivity.

It is difficult to overestimate the importance of addressable complexity: all macroscopic 'machines' consist of many distinct parts that need to be assembled into a unique spatial pattern. If addressable complexity can be developed to the point where nanoscale objects (such as metal or semiconductor nanoparticles, or molecular building blocks) can assemble spontaneously into a predetermined three-dimensional arrangement, the road is open to the design of intricate machines at the nanoscale. Yet one should always remember that natural evolution got there first: biomolecules such as proteins and RNA form complex, addressable three-dimensional structures by hierarchical design. Not surprisingly, there is a close analogy between addressable self-assembly and protein folding. The ways in which the protein-folding process is steered may thus provide inspiration for non-protein-based self-assembly. ❐

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