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Nature of the glassy phase of RNA secondary structure

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Abstract. – We characterize the low-temperature phase of a simple model for RNA secondary structures by determining the typical energy scale $E(l)$ of excitations involving l bases. At low enough temperatures, including $T = 0$, we find a scaling law $E(l) \sim l^{\theta}$ with a small exponent θ. Above a critical temperature, there is a different phase characterized by a relatively flat free-energy landscape resembling that of a homopolymer with a scaling exponent $\theta = 1$. These results strengthen the evidence in favour of the existence of a glass phase at low temperatures.

Introduction. – The folding of RNA or single stranded DNA as described by its secondary structure is both a relevant problem in molecular biology and a challenging task for the statistical mechanics of disordered systems. Several authors [1–6] have recently addressed the topic and put forward some evidence for the existence of a glassy phase at low temperatures. Numerical studies of the specific heat demonstrate the existence of a higher-order phase transition [2]. The nature and properties of the low-temperature phase are less clear because of large finite-size corrections. While the overlap distribution is certainly broad for systems of up to 1000 bases [1, 2], indicating a kind of glassy phase, its asymptotic behaviour for long sequences cannot be deduced reliably from the present simulations [1–4]. Bundschuh and Hwa [5, 6] have recently argued in favour of the existence of a glass phase. They showed analytically that in the disordered case the asymptotic pre-exponential scaling of the partition function cannot be the same as for homogeneous RNA at low temperatures. They also showed that the system of two attractively coupled replicas of the same disordered sequence exhibits a phase transition from a strongly coupled low-temperature phase to a phase at high temperatures where the replicas are essentially independent. Both results favour the existence of a glass transition at finite temperature, but a rigorous proof is still missing. Numerically, the same authors characterize the RNA conformation via the free-energy cost of an imposed pairing (pinching) of two bases. Concentrating on the largest possible pinching excitations in the ground state of a given RNA sequence, they argue in favour of an excitation energy scale that grows logarithmically with the number N of bases in the sequence, a weak power law not being ruled out. However, it is not clear in what sense the excitations created by a single pinch are typical.

In this paper, we propose a different numerical method to study the scale dependence of excitations as was originally introduced in the context of spin glass models [7–9]. The aim is to determine the typical free-energy scale $E(l)$ of excitations involving the bonds of l bases. Rather than changing boundary conditions via pinching, we introduce a perturbation in the bulk which allows for a better control of the actual size of excitations.

We find that the low-temperature regime is governed by excitations which scale as $E(l) \sim l^{\theta}$, where $\theta \approx 0.23$ while the high-temperature phase behaves like a homopolymer with scaling exponent $\theta = 1$. The change of θ indicates a phase transition between a liquid-like high-temperature phase and a strongly correlated glass-like phase at low temperature. In the former, excitations consist of independent rearrangements of individual bases, and the paired pieces of the polymer can slide along each other, while in the latter the system is locked in a favourable secondary structure, and low-lying excitations involve correlated rearrangements of bonds. Note that our description is restricted to the thermodynamic and static properties of RNA. In particular, within our approach we cannot deal with the dynamics of RNA which is expected to be very slow in the low-temperature phase [10].

The model. – The RNA strand is characterized by its (quenched) base sequence, real RNA being composed of the four constituents A, C, G and U. The single-stranded polymer will fold back onto itself to form local double helices of stacked base pairs as found in double-stranded DNA. The pattern of base pairings is known as the secondary structure of RNA. The Watson-Crick base pairs A-U and C-G have the strongest tendency to bind, and in a first approximation one can neglect other pairings. In this paper we concentrate on the secondary structure without taking into account the three-dimensional ternary structure of the polymer whose typical energy scale is significantly lower than that of the base pairing [6, 11].

The glass phase which we will describe exists at the level of the secondary structure. One might imagine another glass phase appearing at the level of the ternary structure, in the form of the possible existence of many metastable spatial arrangements of the molecule, while the secondary structure would be unique. We do not address this question here.

Only two restrictions from the spatial structure are retained: The rigidity of the polymer chain is taken into account by requiring a minimal distance $|j - i| \geq s$ between two bases forming a bond to avoid very small loops of the linking strand. Furthermore, pairings of bases $\{i, j\}$ and $\{k, l\}$ with $i < k < j < l$ are known to be very rare in real RNA for topological reasons. We exclude such pseudoknots altogether in this paper as they can be regarded as a small perturbation. They could in principle be taken into account systematically, using the approach of [12].

To simplify the problem even further we consider a variant of the model defined in [2] with sequences $(b_i)_{i=1,\ldots,N}$ of only two different species, $b_i = A$ or B, with bond energies $e(A, A) = e(B, B) = -1$ and $e(A, B) = e(B, A) = -2$, which is expected to capture the essential physics of RNA. To avoid an artifact of the two-letter model for $s = 1$ (see [6]), we choose $s = 2$ as in earlier work [2]. A natural interpretation of this model is that A and B correspond to small subsequences of a real RNA strand and the energies describe their effective pairing affinities. To mimic the fluctuations of the latter we add a noise to all bond energies, $e_{i,j} \to e_{i,j} + \eta_{i,j}$, where $e_{i,j} = e(b_i, b_j)$ and $\eta_{i,j}$ is a uniformly distributed variable in $[-1/2, 1/2]$. This lifts the exact degeneracy and ensures that the ground state is unique, which is certainly true in real RNA (or when using more realistic rules for secondary-structures energies), and is also useful technically. In parallel, we studied models with different base pairing energies, and with couplings $e_{i,j}$ that are independently drawn from a given continuous distribution without reference to a base sequence. The results were qualitatively the same in all models.

Taking the energy of a secondary structure $\mathcal{S}$ to be the sum of pairing energies, $H(\mathcal{S}) = \sum_{\{i,j\}\in\mathcal{S}} e_{i,j}$, the partition function of an RNA strand with N bases is given by

$$Z_N = \sum_{\mathcal{S}_N} \exp[-\beta H(\mathcal{S}_N)], \tag{1}$$

where the sum extends over all permissible secondary structures $\mathcal{S}_N$. Let us represent a secondary structure $\mathcal{S}$ by the set of numbers $\{p_i\}$ ascribing to each base i the base $p_i = j$ which it is paired to, or $p_i = -1$ if it is unpaired. We can then define an overlap between two secondary structures $\mathcal{S}_\alpha$ and $\mathcal{S}_\beta$ (for the same base sequence) as

$$q^{\alpha\beta} = \frac{1}{N}\sum_{i=1}^{N} \delta_{p_i^\alpha p_i^\beta}\,, \tag{2}$$

which is normalized to $q^{\alpha\alpha} = 1$.

Earlier investigations [1,2] on very similar models concentrated on the probability distribution of the overlap, $P(q)$, which was found to exhibit non–self-averageness, *i.e.*, $P(q)$ depends on the realization of the sequence disorder. Such properties are interpreted as signatures [13] of a glass phase since they require correlations over large parts of the system, implying a divergent correlation length in the low-temperature phase.

However, from the numerical data it was not clear whether or not in the thermodynamic limit $P(q)$ tends to a single delta peak, $\delta(1-q)$, or to a nontrivial function as in mean-field spin glasses. The latter would imply the existence of arbitrarily large excitations of energy $O(1)$ and thus a free-energy exponent $\theta = 0$. For positive θ, however, the ground state dominates at sufficiently low temperature and the overlap is peaked at $q = 1$ in the thermodynamic limit. The system can nevertheless possess a glass phase where favourable free-energy valleys are separated by high barriers, but differ in free energies by terms of order N^θ. This is what happens, for instance, in the case of a directed polymer in random media (DPRM) [14], where $\theta = 1/3$ in $1+1$ dimensions, and we shall show below that the situation is similar in our RNA model at low temperatures. (Let us notice that, in the case of special sequences made up of A and G in the first half of the sequence and C and U in the second half, the RNA model can be mapped onto the DPRM [15].) In such a case, the ϵ-coupling method described below is a choice method to detect the glass phase and to compute θ.

ϵ-coupling at $T = 0$. – Our approach allows a rather direct analysis of the low-lying energy landscape. The basic idea is to introduce a small perturbation in the bulk which repels the system from its ground state $\mathcal{S}_0$ [9,16]. More precisely, one considers the new Hamiltonian

$$H'(\mathcal{S};\epsilon) = H(\mathcal{S}) + \epsilon q(\mathcal{S},\mathcal{S}_0)\,, \tag{3}$$

where the repulsive coupling $\epsilon > 0$ will be tuned appropriately with system size. The energy of the original ground state is increased by ϵ whereas every other state is shifted by a smaller amount. The ground state $\mathcal{S}_\epsilon$ of $H'(\mathcal{S};\epsilon)$ is a low-lying excitation of the original system and has the largest distance $1 - q(\mathcal{S}_\epsilon,\mathcal{S}_0)$ from the ground state at the given excitation energy.

Let us suppose that the typical energy scale of excitations involving the change of the pairing of l bases is $E(l) \sim l^\theta$, or more precisely, that the disorder-averaged probability distribution of energies obeys a scaling law $P[E(l)] = \frac{1}{l^\theta} f\left[\frac{E(l)}{l^\theta}\right]$. Under the assumption that $f(0)$ is finite and $\theta < 1$, one expects the average fraction of bases involved in an excitation to scale as

$$\overline{1 - q(\mathcal{S}_\epsilon,\mathcal{S}_0)} \sim \int_0^{\epsilon/N^\theta} f(E)\mathrm{d}E\,, \tag{4}$$

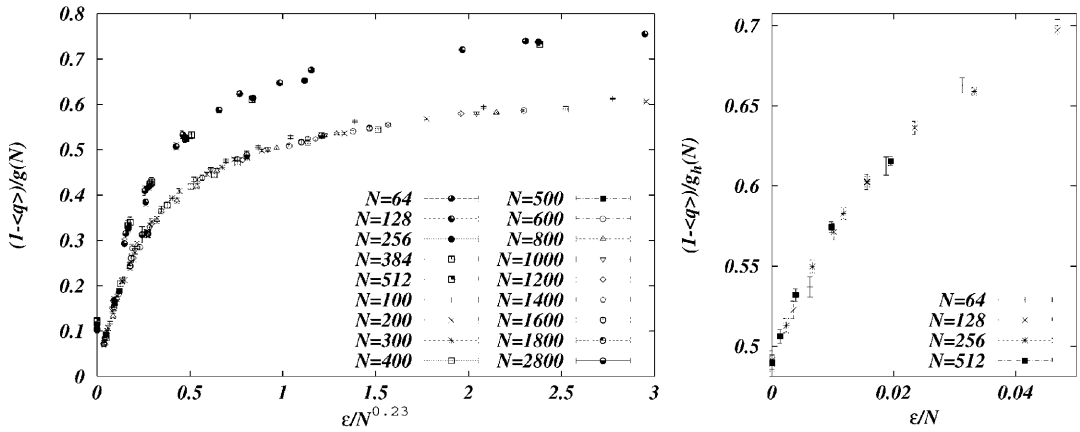

Fig. 1 – Left: scaling plot for ϵ-coupling at $T = 0$ and $T = 0.05$ (shifted vertically by 0.3) with $\theta = 0.23$, giving the distance between the coupled secondary structures *vs.* the strength of the repulsion in reduced units. Right: scaling plot at $T = 0.25$ with $\theta = 1$.

since large-scale excitations of the order of the system size N dominate the disorder average (indicated by the overbar). Note that $\theta < 1$ implies that, for fixed l, excitations composed of several independent "elementary" excitations are usually higher in energy so that the contribution of "elementary" excitations dominates. As we shall see, the data fits well to the more general dependence

$$\overline{1 - q(\mathcal{S}_\epsilon, \mathcal{S}_0)} = g(N)\Phi\left(\frac{\epsilon}{N^\theta}\right), \tag{5}$$

where $g(N)$ has been introduced to account for finite-size effects and is subject to two boundary conditions: For $\epsilon \gg N^\theta \gg 1$, $\overline{q}$ vanishes, and thus $g(N \to \infty) = 1/\Phi(\infty) \equiv 1$. On the other hand, for $\epsilon \ll N^\theta$ and small N one has to recover a behaviour linear in ϵ/N^θ which implies that $g(N \to 0) \to$ const and Φ behaves linearly.

The algorithmic implementation of ϵ-coupling is rather straightforward. The ground state of a particular realization of $e_{i,j}$ can be found recursively in $O(N^3)$ time [1, 11]. The new Hamiltonian (3) is equivalent, up to an irrelevant constant, to a change of the bond energies and the new ground state can be found in the same way as before. We have used 100 to 1000 samples for sizes ranging from 100 to 2800 and with ϵ ranging from 0.2 to 10.0. In fig. 1 we have recast our data into a scaling plot using the trial function $g(N) = 1 + c/(1 + N/N^*)$ for the finite-size effects. We found an optimal value $\theta = 0.23 \pm 0.05$ for the energy exponent, while typical values for the parameters of $g(N)$ are $c \approx 0.6$ and $N^* \approx 300$–1000. We also tried to collapse the curves with scaling variables $\epsilon/\phi(N)$, where $\phi(N) = \log(N/N^*)$ as suggested in [6], or $\phi(N) = 1 - N^*/N + c(N^*/N)^2$. Both possibilties could not be ruled out completely with the present data; however, the power law leads to better values of χ^2. When the range of $\overline{1-q}$ is restricted to small values (< 0.4), the finite-size corrections $g_h(N)$ can be neglected, and the fit yields values of $\theta \approx 0.35$ as in ref. [17].

A better understanding of the finite-size corrections would thus be needed in order to determine the precise value of the θ exponent. At the present stage, taking into account the uncertainty about systematic errors related to the choice of fitting schemes, our data favour a value of θ in the range 0.15–0.40, but we cannot rule out a scenario with $\theta = 0$. For models with different pairing energies we obtained similar results, favouring a power law for the scaling of excitation energies, with exponents in the above-mentioned range of uncertainty.

ϵ-coupling at finite temperature. – Coupling two copies of the system can also be used in its original form at finite temperature [7,8]. We consider two RNA strands with the same random sequence coupled by the Hamiltonian

$$H_{\rm tot}(\mathcal{S}_1,\mathcal{S}_2;\epsilon) = H(\mathcal{S}_1) + H(\mathcal{S}_2) + \epsilon q(\mathcal{S}_1,\mathcal{S}_2). \tag{6}$$

The thermal average of the overlap as a function of ϵ is given by

$$\langle q\rangle(\epsilon) = \frac{\sum_{\mathcal{S}_1,\mathcal{S}_2} q(\mathcal{S}_1,\mathcal{S}_2)\exp[-\beta H_{\rm tot}(\mathcal{S}_1,\mathcal{S}_2;\epsilon)]}{\sum_{\mathcal{S}_1,\mathcal{S}_2}\exp[-\beta H_{\rm tot}(\mathcal{S}_1,\mathcal{S}_2;\epsilon)]} = \frac{\langle q(\mathcal{S}_1,\mathcal{S}_2)\exp[-\beta\epsilon q(\mathcal{S}_1,\mathcal{S}_2)]\rangle_{1,2}}{\langle\exp[-\beta\epsilon q(\mathcal{S}_1,\mathcal{S}_2)]\rangle_{1,2}}\,. \tag{7}$$

Here, $\langle\rangle$ denotes the average over the Gibbsian ensemble of the coupled-two-replica system while $\langle\rangle_{1,2}$ denotes the average with independent Boltzmann weights for the two replicas. Note that the partition function corresponding to the coupled Hamiltonian (6) is simply related to the Laplace transform of $P(q)$ with respect to $\beta\epsilon$. We can rewrite eq. (7) as

$$\langle q\rangle(\epsilon) = -\frac{1}{\beta}\frac{\partial}{\partial\epsilon}\ln\left\{\left\langle\sum_{\mathcal{S}_2}\exp[-\beta H(\mathcal{S}_2) - \beta\epsilon q(\mathcal{S}_1,\mathcal{S}_2)]\right\rangle_1\right\} \equiv -\frac{1}{\beta}\frac{\partial}{\partial\epsilon}\ln\left[\langle Z_2(\epsilon;\mathcal{S}_1)\rangle_1\right]\,, \tag{8}$$

where the average $\langle\rangle_1$ extends only over the first replica. The averages over the secondary structure of a single RNA strand are calculated by sampling the Gibbs ensemble as in [1]: The partition functions $Z_{i,j}$ corresponding to connected substrands $\{i,j\}$ are calculated recursively and can then be used to generate secondary structures with their corresponding Boltzmann weight. Since the coupling is not expected to alter the single sequence statistics significantly, we approximated the right-hand side of eq. (8) by calculating an average over 20 randomly sampled structures $\mathcal{S}_1$ for each of which $Z_2(\epsilon;\mathcal{S}_1)$ is calculated exactly. We verified that the results of more extensive samplings lie within the error bars of the disorder average.

In fig. 1 we plot the data obtained for $T = 0.05$ and $T = 0.25$. The data collapse works best with a free-energy exponent $\theta = 0.2$–0.3 at $T = 0.05$ which coincides with the zero-temperature exponent. For $T = 0.25$ we have to choose $\theta = 1$ to superpose all the curves. This is the same exponent that one finds in the case of homogeneous RNA, as is shown in the next section. $\theta = 1$ can no longer be interpreted as a free-energy exponent at high temperatures. It can be understood in terms of a flat free-energy landscape and uncorrelated behaviour of individual bases. A study of the homogeneous case is instructive in this respect.

ϵ-coupling in the homogeneous case. – Let us consider the problem of RNA with homogeneous base pairing energy $e_{i,j} \equiv e$. In this case, it is possible to calculate analytically the asymptotic ($N \to \infty$) limit of the partition function of two coupled replicas with Hamiltonian (6) in close analogy to [6]: For each configuration of the two replicas we determine the common bonds and the bases which are unpaired in both sequences. The contribution of these common elements is split into a connected part that vanishes for $\epsilon = 0$, and a disconnected part corresponding to uncoupled strands. Thus, the contribution of a configuration with n common elements (bonds or unpaired bases) is split into a sum of 2^n terms. In each such term we determine the m (connected) common bonds and the f common unpaired bases which are not embraced by a connected common bond. Summing over all possibilities to arrange those $m + f$ connected common elements on the RNA strand we arrive at a recursion relation for the total partition function which reads

$$Z_{\rm tot}(N) = \sum_{f\geq 0}\sum_{m\geq 0}\sum_{l_1\ldots l_m\geq 2}\binom{m+N-\sum l_i}{m,\,f} Z_1^2\left(N - \sum_{i=1}^{m} l_i - f\right) g_u^f \prod_{i=1}^{m}\left[g_d Z_{\rm tot}(l_i - 2)\right], \tag{9}$$

where $g_u = e^{-\beta\epsilon/N} - 1$ and $g_d = e^{-2\beta e}(e^{-2\beta\epsilon/N} - 1)$ are the connected couplings. The interior of each connected common bond of length l_i is treated as a two-replica system with N replaced by $l_i - 2$. Note that here we use $s = 1$ for the smallest permissible loop. $Z_1(N)$ is the partition function of one replica with N bases. The factor $Z_1^2(N - \sum l_i - f)$ arises from all bonds that can be distributed on the remaining free part of the strands outside the m connected common bonds, excluding the f connected unpaired bases. The combinatorial factor counts the possibilities to align m connected common bonds, f unpaired common bases and $N - \sum l_i - f$ free bases. Of course, we have to require $\sum l_i + f \leq N$.

Let us fix the values of g_u and g_d for a moment and introduce the generating function of $Z_{\rm tot}$ for which we can derive a recursion relation using (9),

$$\Xi(\zeta) = \sum_{N=0}^{\infty} Z_{\rm tot}(N)\zeta^N = \frac{1}{1 - g_d\zeta^2\Xi(\zeta) - g_u\zeta}\Xi_2\left(\frac{\zeta}{1 - g_d\zeta^2\Xi(\zeta) - g_u\zeta}\right). \tag{10}$$

Here, $\Xi_2(\zeta) = \sum_{N=0}^{\infty} Z_1^2(N)\zeta^N$ denotes the generating function of $Z_1^2(N)$. $Z_1(N)$ satisfies the recursion relation,

$$Z_1(N) = Z_1(N-1) + \sum_{k=0}^{N-2} g_0 Z_1(k) Z_1(N-k-2), \tag{11}$$

with $g_0 = e^{-\beta e}$, and the corresponding generating function $\Xi_1(\zeta)$ can be obtained explicitly,

$$\Xi_1(\zeta) = \frac{1 - \zeta - \sqrt{(1-\zeta)^2 - 4g_0\zeta^2}}{2\zeta^2 g_0}. \tag{12}$$

The behaviour of $Z_1(N)$ for large N can be derived from this expression by inverse Laplace transform, see [6, 18, 19]. Asymptotically, one finds $Z_1(N) = c\zeta_1^{-N}/N^{3/2}$, where $\zeta_1 = (1 + 2\sqrt{g_0})^{-1}$ is the smallest singularity of $\Xi_1(\zeta)$. Similarly, the smallest singularity ζ_* of $\Xi(\zeta)$ determines the leading behaviour of $Z_{\rm tot}$. One can check that, since g_d is negative, ζ_* is always determined by the singularity of Ξ_2 on the RHS of eq. (10), *i.e.*, $\zeta_*/[1 - g_d\zeta_*^2\Xi(\zeta_*) - g_u\zeta_*] = \zeta_1$, or, explicitly,

$$\zeta_* = \zeta_1/[1 + g_d\zeta_1^2\Xi(\zeta_1) + g_u\zeta_1]. \tag{13}$$

Asymptotically, the two-replica partition function behaves as $Z_{\rm tot}(N) = \tilde{c}\frac{\zeta_*^{-N}}{N^{3/2}}$. We can now calculate $\langle q\rangle(\epsilon)$ by taking the logarithmic derivative of $Z_{\rm tot}(N)$ recalling the dependence of g_u and g_d on ϵ/N,

$$\langle q\rangle(\epsilon, N) = -\frac{\partial \ln Z_{\rm tot}(N)}{\beta\partial\epsilon} \approx \frac{N}{\beta}\frac{\partial \ln \zeta_*}{\partial\epsilon} = \frac{2g_0^2\zeta_1^2\Xi_2(\zeta_1)e^{-2\beta\epsilon/N} + \zeta_1 e^{-\beta\epsilon/N}}{1 + g_d\zeta_1^2\Xi_2(\zeta_1) + g_u\zeta_1}. \tag{14}$$

From eq. (14) it is clear that $\langle q\rangle = q(\epsilon/N)$ and thus $\theta = 1$ in the homopolymer. We can understand this scaling behaviour as a lack of long-range correlations in the system. (A simple example of such a behaviour is the case of N uncoupled Ising spins in a random field under ϵ-coupling.) In order to affect the overlap significantly, one has to introduce an extensive perturbation which corresponds to a finite force acting on each base and typically leads to a large number of independent local rearrangements.

Phase transition. – We will now use the scaling exponent θ to define an order parameter for the presumed phase transition in the disordered system. Consider the effect of a small extensive coupling between two replicas, *i.e.*, $\epsilon = \delta N$. In a phase with $\theta < 1$ where typical

excitation energies are subextensive ($o(N)$), the coupling always dominates in the thermodynamic limit. The replicas will have no overlap ($q = 0$) for a repulsive coupling $\delta > 0$, while they are locked together ($q = 1$) when the coupling is attractive ($\delta < 0$). However, if $\theta = 1$ an extensive coupling is a marginal perturbation. In the homogeneous case we can directly check from eq. (14) that small perturbations have a negligible effect, and $\langle q \rangle$ is continuous as $\delta \to 0\pm$. From the numerical data in fig. 1 we see that the same is true in the high-temperature phase of disordered sequences which leads us to define the order parameter

$$\phi = \lim_{\delta \to 0} \left\{ \lim_{N \to \infty} [\overline{q}(\epsilon = -\delta N; N) - \overline{q}(\epsilon = \delta N; N)] \right\}. \tag{15}$$

For a homopolymer $\phi \equiv 0$ at all temperatures. For disordered sequences ϕ jumps discontinuously at the critical temperature from 0 in the high-temperature phase to $q_{\max} - q_{\min} = 1$ in the glassy phase. This provides a precise mathematical definition of the transition temperature.

Conclusion. – We have studied a simple model for the folding of RNA, taking as a probe the susceptibility to the introduction of a repulsion between two identical clones of the system. Our method clearly distinguishes a low-temperature glassy regime, identical to the zero-temperature case, where the excitation energies scale with a power law of the length, with a small scaling exponent. On the contrary, the high-temperature liquid-like phase is found to behave similarly to a homopolymer, both having a relatively flat free-energy landscape and no long-range correlations in the base-pairing pattern. The result for the exponent θ gives way to the definition of an order parameter which jumps discontinuously at the critical temperature.

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