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Heat capacities of globular proteins

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Abstract

The heat capacities of globular proteins due to residue fluctuations are studied theoretically based on a Gaussian network model. It is found that the heat capacities for globular proteins as a function of a scaled temperature almost follow a universal curve in spite of their different sizes, shapes, and architectures. From the heat capacity curve at low temperatures, we can derive the spectral dimension of globular proteins, which is found to be larger than 2. This result implies that globular proteins behave dynamically as objects with dimension between 2 and 3.

Proteins are linear polymers congregated from 20 amino acid monomers, playing an important role in almost all biological systems. Owing to the finite temperature effects, the constituent residues fluctuate near their native positions [1]. These residue fluctuations are crucial for enzyme catalysis and for biological activity as well [2, 3]. As a result, there has been an increasing interest in protein dynamics in recent years. It has been found that there exist some strong correlations between residue fluctuations and protein functions [2].

Many interesting dynamical properties of proteins have been studied. Although proteins show diversified structures and sizes, a few universal physical behaviours in globular proteins have been revealed. For instance, we found that the participation ratio of residue fluctuation modes versus frequency in globular proteins is similar for all globular proteins [4], indicating a universal behaviour of localization of residue fluctuations. From a physical point of view, it is interesting to study the heat capacities of proteins, from which we can get insight into both the thermal and likely other physical properties of proteins. In the present work, we study theoretically the heat capacities of globular proteins due to residue fluctuations. A universal behaviour of the heat capacities in globular proteins is found.

A Gaussian network model [5] (GNM) is adopted in the present work to study the heat capacities of globular proteins. Within the frame work of this model, proteins are modelled as elastic networks whose nodes are residues linked by inter-residue potentials that stabilize the folded conformation. The residues are assumed to undergo Gaussian-distributed fluctuations about their native positions. No distinction is made between different types of residues.

Table 1. Proteins used in calculations.

Protein name	PDB code	Reference
Cysb	1al3	[9]
LAO	2lao	[10]
PBGD	1pda	[11]
Myoglobin	1bvc	[12]
Lysozyme	166l	[13]
Thermolysin	5tln	[14]

A single generic harmonic force constant is used for the inter-residue interaction potential within a cutoff range. The Hamiltonian within the GNM can be written as [5]

$$H = \tfrac{1}{2}\gamma \left[\Delta \mathbf{R}^{\mathrm{T}} \left(\mathbf{\Gamma} \otimes \mathbf{E}\right) \Delta \mathbf{R}\right], \tag{1}$$

where γ is the harmonic force constant; $\{\Delta \mathbf{R}\}$ represents the $3N$-dimensional column vectors of fluctuations $\Delta \mathbf{R}_1, \ldots, \Delta \mathbf{R}_N$ of the C^α atoms, where N is the number of residues; $\mathbf{E}$ is the third-order identity matrix; the superscript T denotes the transpose; $\otimes$ stands for the direct product, and $\mathbf{\Gamma}$ is the $N \times N$ Kirchhoff matrix [6] with the elements given by

$$\Gamma_{ij} = \begin{cases} -H(r_{\mathrm{c}} - r_{ij}), & i \neq j, \\ -\displaystyle\sum_{i(\neq j)}^{N} \Gamma_{ij}, & i = j. \end{cases} \tag{2}$$

Here, r_{ij} is the separation between the ith and jth C^α atoms, $H(x)$ is the Heaviside step function, and r_{c} is the cutoff distance outside of which there is no inter-residue interaction. The ith diagonal element of Γ characterizes the local packing density or the coordination number of residue i. It has been found that the GNM can give a satisfactory description of the residue fluctuations of folded proteins [5, 7].

Based on the classical normal mode analysis, the force constant matrix is given by $\gamma\Gamma$. The frequency of fluctuation modes is obtained from $\omega_i = \sqrt{\gamma \lambda_i}$, where λ_i is the ith eigenvalue of the matrix Γ. In our calculations, the cutoff distance is taken to be $r_{\mathrm{c}} = 7$ Å, as adopted in previous studies [4, 5]. The harmonic force constant γ is determined by fitting to the experimental mean-square fluctuations. Within the GNM, one obtains N residue fluctuation modes.

The total thermal energy due to residue fluctuations is given by [8]

$$E = \sum_{i=2}^{N} \frac{\hbar\omega_i}{\mathrm{e}^{\hbar\omega_i/k_{\mathrm{B}}T} - 1}, \tag{3}$$

where k_{B} is the Boltzmann constant. The first mode is not included in the summation since its frequency is zero. The heat capacity is found by differentiation of the total thermal energy with respect to temperature [8], namely

$$C_V(T) = k_{\mathrm{B}} \sum_{i=2}^{N} \left(\frac{\hbar\omega_i}{k_{\mathrm{B}}T}\right)^2 \frac{\mathrm{e}^{\hbar\omega_i/k_{\mathrm{B}}T}}{\left(\mathrm{e}^{\hbar\omega_i/k_{\mathrm{B}}T} - 1\right)^2}. \tag{4}$$

The heat capacity can then be calculated from the obtained residue fluctuation modes for any given temperature. Globular proteins used in the calculations are listed in table 1.

It is found that the heat capacity is similar for globular proteins with similar structures. It is different for proteins with different structures, especially at low temperatures. Heat capacities for all proteins become nearly identical at high temperatures, approaching the classical value, as expected. The different heat capacity for different proteins at low temperatures is not

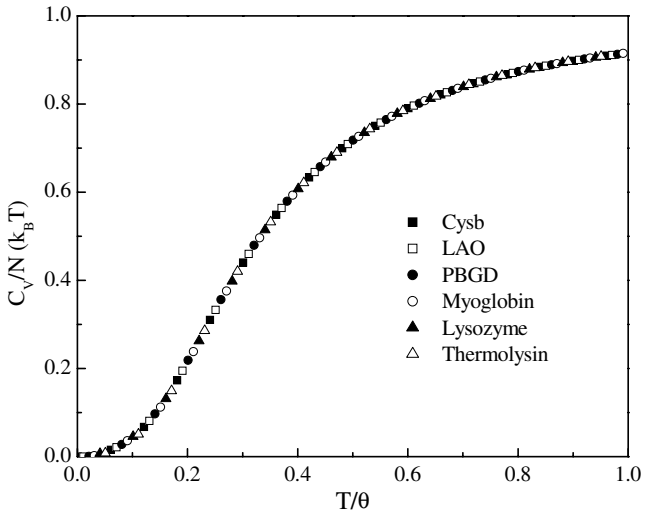

Figure 1. Calculated heat capacities for several globular proteins as a function of the scaled temperature T/θ.

surprising since different proteins have rather different topological structures. However, if we scale the temperature by a factor θ, it is found that the heat capacities of different globular proteins, as a function of the scaled temperature T/θ, collapse almost into a universal curve, as shown in figure 1. The scaling factor θ is defined by

$$\theta = \frac{1}{(N-1)k_{\mathrm{B}}} \sum_{i=2}^{N} \hbar\omega_i, \tag{5}$$

with a dimension of temperature. It is surprising that the heat capacities of globular proteins exhibit a universal behaviour since their topological structures and sizes are rather different. This may reflect the dynamical similarities among globular proteins or even their statistically structural similarities.

To get insight into dimensional effects on heat capacity, we also study the heat capacities of a linear-chain (1D), square lattice (2D), and cubic lattice (3D) model proteins, shown in figure 2. Only the interactions between the nearest-neighbour residues are considered. The difference of heat capacity mainly occurs at low temperatures. For lattice mode proteins at a given scaled low temperature, the heat capacity of the 3D lattice is the largest, that of the 1D lattice is the smallest, and the 2D lattice in between. At scaled low temperatures, the heat capacities for globular proteins fall in between 2D and 3D lattices, smaller than that of the 3D lattice, but larger than that of the 2D lattice.

It is known that the behaviour of the heat capacity at low temperatures is determined by the behaviour of the density of states $g(\omega)$ at low frequencies. The density of states at low temperatures is given by [15]

$$g(\omega) \propto \omega^{d_{\mathrm{s}}-1}, \tag{6}$$

where d_{s} is the spectral dimension. As a result, the heat capacity at low temperature should follow

$$C_V(T) \propto T^{d_{\mathrm{s}}}. \tag{7}$$

Although the heat capacities of globular proteins exhibit almost a universal behaviour, there does exist a small difference at scaled low temperatures. This leads to different d_{s} for

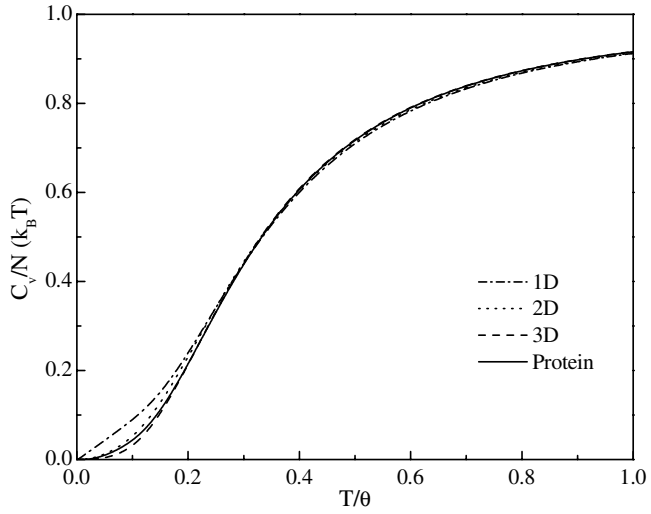

Figure 2. Calculated heat capacities for 1D, 2D, 3D lattice model proteins, and globular proteins as a function of the scaled temperature T/θ.

different proteins. From the heat capacity curve, one can derive the spectral dimension d_s. The obtained d_s for different globular proteins studied is not much diversified, varying in a small range from 2.1 to 2.4. In [16], d_s, derived from the density of states, is 2 for globular proteins. Thus, the author suggested that globular proteins would behave as 2D objects. In [5], the derived d_s from the density of states calculations is about 1.63, much smaller than both our prediction and that in [5]. The value of $d_s \sim 1.63$ in [5] indicates that globular proteins behave dynamically as objects with dimension between 1 and 2. This might be not physically reasonable since globular proteins are among the most densely packed organic molecules in nature. From our results, we may conclude that globular proteins behave as objects with dimension between 2 and 3, but close to 2 since d_s lies between 2.1 and 2.4.

In summary, based on the GNM model, we have studied theoretically the heat capacities of globular proteins due to residue fluctuations. It is found that the heat capacities of globular proteins as a function of the scaled temperature collapse almost into one curve, indicating a universal and similarly dynamical behaviour. The derived spectral dimension from the heat capacity curves for different globular proteins is rather convergent, varying in a small range from 2.1 to 2.4. This result suggests that globular proteins would behave dynamically as objects with dimension between 2 and 3, but close to 2.

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