Hidden Structure in Protein Energy Landscapes

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Protein activity is controlled by dynamical transitions among conformational substates [1]—the transitions may be understood in terms of motions on an energy landscape [2]. Substates correspond to local minima in the energy landscape, and transitions correspond to the hurdling of barriers between minima. The shape of basins strongly influences the kinetics of transitions, which in turn determine the time scales for important processes such as protein folding and communication of allosteric effects.

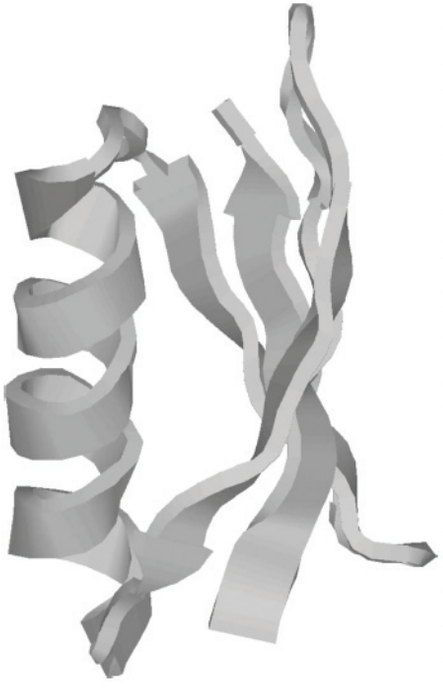

Fig. 1. (left) Schematic illustration of the immunoglobulin-binding domain of Streptococcal *protein G (GB1).*

To gain insight into protein energy landscapes, we performed a computational study to investigate diversity among basins in the energy landscape of a coarse-grained model of the immunoglobulin-binding domain of *Streptococcal* protein G (GB1) (Fig. 1) [3]. We found that different basins had different curvatures in the neighborhood of the minimum. The differences were characterized using the free energy of small vibrations about the minimum (Fig. 2). The spectrum of vibrational free energies produced a density of minima versus energy, resembling that of a structural glass (Fig. 3). Interestingly, both the vibrational free energy and the potential energy of a minimum could be simply modeled in terms of the native contacts that are lost in moving the protein from the native structure to the minimum (Fig. 4).

Studies of energy landscapes frequently assume that different basins have a similar shape. Our finding of diversity in the vibrational free energy of different basins in a model of GB1 challenges this assumption. For the present model, the diversity still exhibits a relatively simple structure, and is consistent with the previously noted similarity between the energy landscapes of proteins and glasses [4]. The vibrational free energy is similar for basins about minima with similar energy, enabling simpler and faster computations of thermodynamic properties using inherent structure theory [5,6]. In addition, the vibrational free energy can be modeled using elementary measures of the network of native contacts, which can be used in theoretical studies of protein energy landscapes. Our methods are extensible to more detailed models of proteins, and we expect them to yield analogous

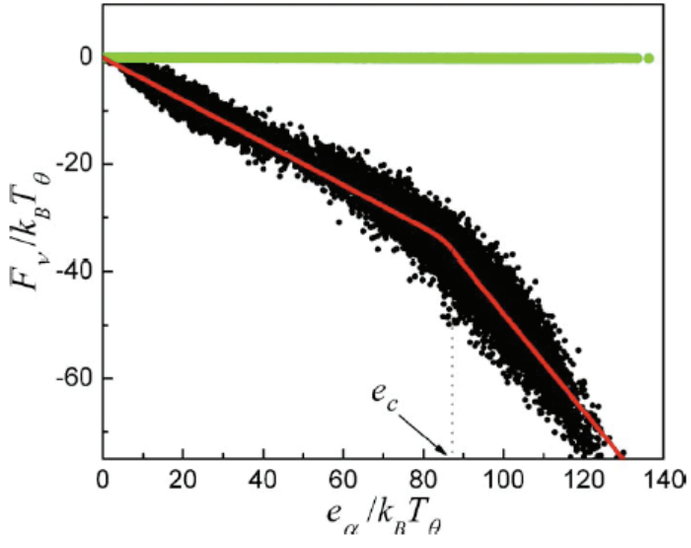

Fig. 2. (right) Vibrational free energies, F_v, of minima versus their potential energies e_a (black points). The contribution from vibrations between bonded atoms is constant (green points following $y = 0$)—the diversity is due to differences in the energetics of perturbing other degrees of freedom.

results in more general applications, revealing relatively simple structures that are hidden in complex protein energy landscapes.

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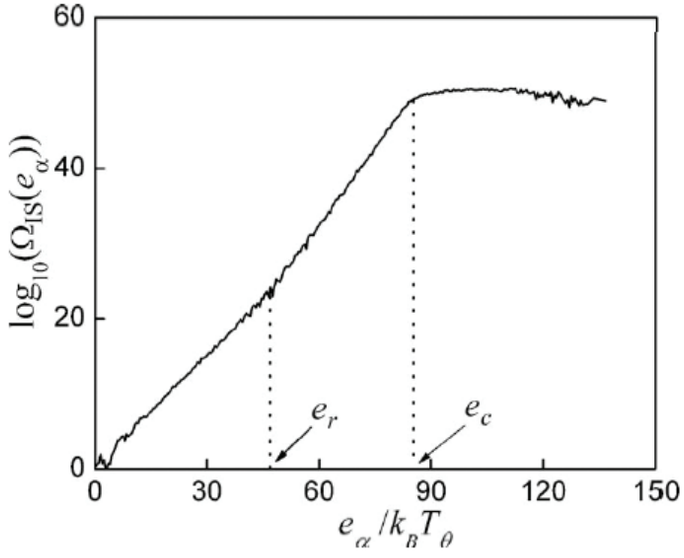

Fig. 3. Density of minima $W_{IS}(e_a)$. The knee at $e_r = 47.4 k_B T$ is due to a change in stress, and the plateau beginning at roughly $e_c = 88.4 k_B T$ is due to a change in rigidity—both are understood in terms of the network of native contacts.

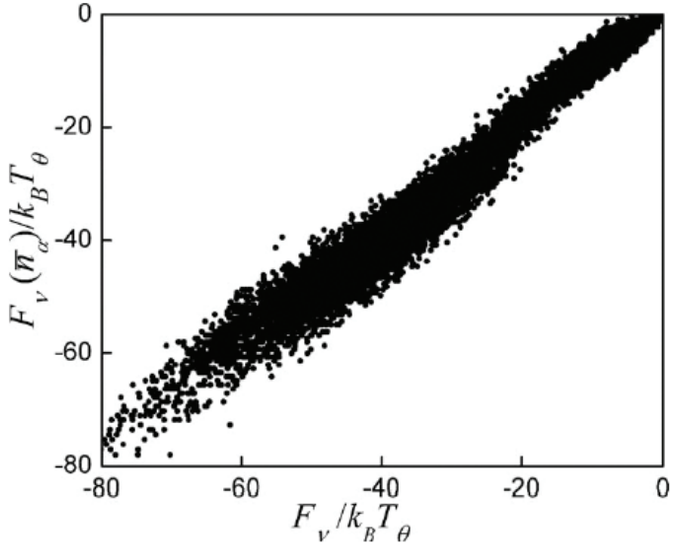

Fig. 4. Comparison of vibrational free energies calculated from the model (y axis) or estimated from numerical simulations (x axis).

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