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Coarse-Grained Lattice Model for Molecular Recognition

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Equilibrium aspects of molecular recognition are investigated using coarse-grained models for the recognition process of two rigid biomolecules. To this end, a two-stage approach consisting of a design and testing step is adopted. Particular attention is paid to the influence of cooperative effects accompanying the association of biomolecules. Cooperativity is found to enhance selectivity. In addition it is discussed that a small number of strong bonds is favoured in flexible complexes compared to a situation with many but weak bonds.

1 Introduction

An understanding of the basic principles of biomolecular recognition, i. e. the ability of a biomolecule to interact specifically with another molecule in the presence of structurally similar rival molecules, is not only important from a scientific point of view but also opens up a wide field of potential biotechnological applications. The recognition process itself is governed by a complex interplay of non-covalent interactions of strengths comparable with the thermal energy thus leading to a complex problem[1,3]. In this context the study of idealised models with methods from statistical physics seems to be particularly adequate.

2 Model and General Approach

In this work we consider protein-protein recognition from a coarse-grained point of view on the level of both the structure of the biomolecules at the mutual interface and the interactions stabilising the complex. The biomolecules are assumed to undergo no refolding during the association process. This is a justified assumption for most protein-protein recognition processes, although notable exceptions do exist[1]. Motivated by the observation that hydrophobicity is the major driving force in molecular recognition[1] we describe the type of the residue at the position $i = 1, \ldots, N$ of the interface by a binary variable[2,3]. Denoting the structure of the target molecule by $\sigma_i \in \{\pm 1\}$ and that of the interaction partner by $\theta_i \in \{\pm 1\}$ we model the energetics at the interface by

$$\mathcal{H}(\sigma, \theta; S) = -\varepsilon \sum_{i=1}^{N} \frac{1 + S_i}{2} \sigma_i \theta_i - J \sum_{\langle ij \rangle} S_i S_j . \tag{1}$$

The variable S_i takes on the two discrete values ± 1 and describes the fit of the shape of the molecules at position i of the interface (on a microscopic level resulting from a rearrangement of the amino acid side chains when the complex is formed[1]). Apart from the direct contact energy with strength ε the model Hamiltonian contains an additional cooperative interaction term where the quality of a residue-residue contact couples onto the structure in its neighbourhood. To study the recognition process between two rigid

biomolecules we adopt a two-stage approach. For a fixed target structure $\sigma^{(0)}$ we first design an ensemble of probe molecules θ at a design temperature $1/\beta_{\mathrm{D}}$ leading to the distribution $P(\theta|\sigma^{(0)}) = \frac{1}{Z_{\mathrm{D}}} \sum_S \exp\left(-\beta_{\mathrm{D}} \mathcal{H}(\sigma^{(0)}, \theta; S)\right)$. In a second step the free energy difference of association at temperature $1/\beta$ is calculated for the interaction of the probe ensemble with the target molecule $\sigma^{(0)}$ and a structurally different rival molecule $\sigma^{(1)}$. In this step the free energy of the interaction of the molecule $\sigma^{(\alpha)}$ with a particular probe structure θ has to be averaged with respect to the distribution $P(\theta|\sigma^{(0)})$. This gives finally the free energy difference $\Delta F = F_{\mathrm{target}} - F_{\mathrm{rival}}$ as a function of the similarity Q between these two molecules, where Q is the number of residues N at the interface minus twice the number of point mutations that have to be carried out to convert the target into the rival. A negative ΔF then signals recognition of the target.

3 Results

It has been argued in the literature for the importance of cooperativity for molecular recognition[4]. In our coarse-grained Hamiltonian (1) cooperativity is taken into account by the second interaction term. The cooperative term rewards additional contacts in the neighbourhood of an already established one. As a consequence the fit of the two biomolecules at the interface is optimised and therefore one can expect an improved recognition ability. An investigation of the influence of this second term using our two-stage approach indeed reveals as shown in figure 1 that an increase of the cooperative interaction constant J significantly increases the recognition ability, i. e. the free energy difference. A value of J comparable to the value of ε already leads to the maximum effect of cooperativity (up to minor finite-size effects).

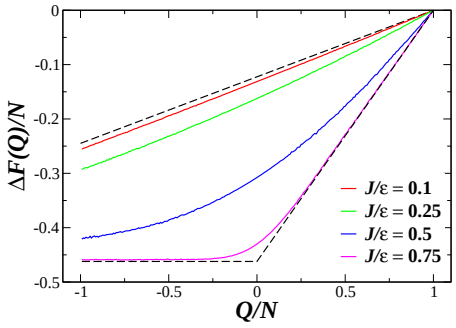

Figure 1. Influence of the cooperativity J on the free energy difference for the association of the probe molecules with the target and the rival molecule as a function of the similarity Q between these two molecules. The upper dashed line corresponds to $J = 0$, the lower one to $J \to \infty$ (in the limit $N \to \infty$).

Investigations of highly flexible antibody-antigen complexes showed that only approximately one quarter of the residue contacts at the interface contribute (significantly) to the binding energy[5] suggesting that in flexible complexes interfaces with a few strong bonds are favoured compared to a situation with many but weak bonds. We address this question of the role of varying bond strengths within our approach by considering a model which

distinguishes only between active residues, i. e. residues that contribute to the binding energy, and inactive ones. On the coarse-grained level this amounts to attributing the values 1 (active) and 0 (inactive) to the structural variables σ_i and θ_i in the Hamiltonian (1). In the following the uncooperative model with $J = 0$ is considered. In order to ensure the stability of the complex the interaction energy has to overcome the thermal energy barrier. On the other hand, however, the interaction energy has to be "small" enough to ensure the required flexibility of the complex. This can be incorporated into our approach by including the constraint that the interaction energy has to be fixed to some (suitable) value. Fixing the number of active residues A by a Lagrange multiplier, the free energy difference ΔF can be calculated as a function of the fraction A/N of active residues. Figure 2 demonstrates that the free energy difference indeed has a minimum at small fractions A/N (fairly insensitive to a variation of the interaction parameters). Our simple coarse-grained model hence predicts that recognition processes which require a certain amount of flexibility are most efficient if only a small number of fairly strong bonds is established across the contact interface as observed in antibody-antigen complexes.

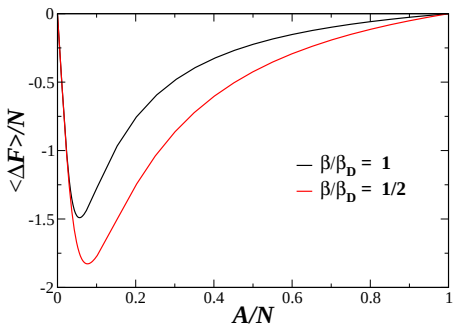

Figure 2. Averaged free energy per site as a function of the fraction A/N of active residues.

Acknowledgements

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