

# A Coarse-Grained Lattice Model for Molecular Recognition

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We present a simple model which allows to investigate equilibrium aspects of molecular recognition between rigid biomolecules on a generic level. Using a two-stage approach, which consists of a design and a testing step, the role of cooperativity and of varying bond strength in molecular recognition is investigated. Cooperativity is found to enhance selectivity. In complexes which require a high binding flexibility a small number of strong bonds seems to be favored compared to a situation with many but weak bonds.

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Living organisms could not function without the ability of biomolecules to specifically recognize each other [1, 2]. Molecular recognition can be viewed as the ability of a biomolecule to interact preferentially with a particular target molecule among a vast variety of different but structurally similar rival molecules. Recognition processes are governed by an interplay of non-covalent interactions, in particular, hydrophobic interactions and hydrogen bonds. Such non-covalent bonds have typical energies of 1-2 kcal/mole (the relatively strong hydrogen bonds may contribute up to 8-10 kcal/mole) and are therefore only slightly stronger than the thermal energy  $k_B T_{\text{Room}} \simeq 0.62$  kcal/mole at physiological conditions. Biomolecular recognition is thus only achieved if a large number of functional groups on the two partner molecules match precisely. This observation has led to a “key-lock” picture: Two biomolecules recognize each other if their shapes at the recognition site and/or the interactions between the residues in contact are largely complementary [3].

In the present Letter, we introduce a coarse-grained approach which allows to investigate this “principle of complementarity” on a very general level, and use it to study the role of different factors for the selectivity of interactions between biomolecule surfaces. Specifically, we analyze two elements that have been discussed in the literature: the cooperativity, and the interplay of interaction strengths. We will show that our model can help to understand some of the features of real protein-protein interfaces.

Previous theoretical studies have mostly dealt with the adsorption of heteropolymers on random and structured surfaces [4–6]. Some works have adapted the random energy model from the theory of disordered systems to the problem of biomolecular binding [7, 8]. In contrast, in the present approach, we consider explicitly systems of two interacting, rigid, heterogeneous surfaces. This is motivated by some basic findings about the biochemical structure of the recognition site, *i.e.*, the contact interface between recognizing proteins. In recent years the structural properties of proteins at the recognition site has been clarified [2, 9, 10]. Although different protein-

protein complexes may differ considerably, a general picture of a standard recognition site containing approximately 30 residues, with a total size of 1200-2000 Å<sup>2</sup> has emerged. Apart from notable exceptions, the association of the proteins is basically rigid, although minor rearrangements of amino acid side-chains do occur [9, 10].

We describe the structure of the proteins at the contact interfaces by two sets of classical spin variables  $\sigma = (\sigma_1, \dots, \sigma_N)$  and  $\theta = (\theta_1, \dots, \theta_N)$ , whose values specify the various types of residues. The set  $\sigma$  characterizes the structure of the recognition site on the target molecule, and  $\theta$  that on the probe molecule, *i.e.*, the molecule that is supposed to recognize the target. The position of site  $i$  on the surfaces can be specified arbitrarily. For simplicity, we assume that the positions  $i$  on both surfaces match, and that the total number of contact residues is equal  $N$  for both molecules. However, we take into account the possibility that the quality of the contact of two residues at position  $i$  may vary, *e.g.*, due to steric hindrances or varying relative alignment of polar moments, caused by minor rearrangements of the amino acid side-chains. This is modeled by an additional variable  $S_i$ ,  $i = 1, \dots, N$ . The total interaction is thus described by a Hamiltonian  $\mathcal{H}(\sigma, \theta; S)$ , which incorporates in a coarse-grained way both the structural properties of the recognition site and the interaction between residues.

To study the recognition process between two biomolecules, we adopt a two-stage approach. We take the structure of the target recognition site,  $\sigma^{(0)} = (\sigma_1^{(0)}, \dots, \sigma_N^{(0)})$ , to be given. In the first step, the probe “learns” the target structure at a given “design temperature”  $1/\beta_D$ . One obtains an ensemble of probe molecules with structures  $\theta$  distributed according to a probability  $P(\theta|\sigma^{(0)}) = \frac{1}{Z_D} \sum_S \exp(-\beta_D \mathcal{H}(\sigma^{(0)}, \theta; S))$ , which depends on the target structure. This first design step is introduced to mimic the design in biotechnological applications or the evolution process in nature. The parameter  $\beta_D$  characterizes the conditions under which the design has been carried out, *i.e.*, it is a Lagrange parameter which fixes the achieved average interaction energy. A similar design procedure has been introduced in studies of protein folding [11] and the adsorption of

polymers on structured surfaces [12]. In the second step, the recognition ability of the designed probe ensemble is tested. To this end the probe molecules are exposed to both the original target structure  $\sigma^{(0)}$  and a competing (different) rival structure  $\sigma^{(1)}$  at some temperature  $1/\beta$ , which in general differs from the design temperature  $1/\beta_D$ . The thermal free energy  $F(\theta|\sigma^{(\alpha)})$  for the interaction between  $\sigma^{(\alpha)}$  ( $\alpha = 0, 1$ ) and a probe  $\theta$  is given by  $F(\theta|\sigma^{(\alpha)}) = -\frac{1}{\beta} \ln \sum_S \exp(-\beta \mathcal{H}(\sigma^{(\alpha)}, \theta; S))$ . Averaged over all probe molecules, we obtain  $\langle F^{(\alpha)} \rangle = \sum_{\theta} F(\theta|\sigma^{(\alpha)}) P(\theta|\sigma^{(0)})$ . The target is recognized if the average free energy difference  $\Delta F = \langle F^{(0)} \rangle - \langle F^{(1)} \rangle$  is negative, *i.e.*, probe molecules exposed to equal amounts of target and rival molecules preferentially bind to the target. Note that our treatment does not account for kinetic effects, only equilibrium aspects are considered.

The association of the proteins is accompanied by a reduction of the translational and rotational entropy. However, these additional entropic contributions to the free energy of association depend only weakly on the mass and shape of the rigid molecules, and can be considered, in a first approximation, to be of the same order for the association with the target and the rival molecule. Thus, these contributions cancel in the free energy difference. Similarly, contributions from the interaction with solvent molecules are also assumed to be of comparable size.

A modified HP-model can serve as a first example to illustrate this general description. In the HP-model, which was introduced originally to study protein folding [13], residues are distinguished by their hydrophobicity only. Hydrophobic residues are represented by  $\sigma_i, \theta_i = +1$ , and polar residues by  $\sigma_i, \theta_i = -1$ . In addition, the variable  $S_i$  describing the (geometric) quality of the contact can take on the values  $\pm 1$  where  $S_i = +1$  models a good contact and  $S_i = -1$  a bad one. Only for good contacts does one get a contribution to the binding energy. The Hamiltonian is then given by

$$\mathcal{H}(\sigma, \theta; S) = -\varepsilon \sum_i \frac{1 + S_i}{2} \sigma_i \theta_i \quad (1)$$

where the sum extends over the  $N$  positions of the residues of the recognition site and  $\varepsilon$  being the interaction constant [14]. Note that a ‘‘good’’ contact can nevertheless lead to an unfavorable energy contribution. For this simple model, the different steps of the two-stage approach described above can be worked out analytically.

First, we analyze the efficiency of the design step by inspecting the achieved complementarities (of interactions) of the designed probe molecules with the target molecule. To this end, we define a complementarity parameter  $K = \sum_i \sigma_i^{(0)} \theta_i$  which ranges from  $-N$  to  $+N$ , with  $K$  close to  $+N$  signaling a large complementarity of the recognition sites. The probability distribution  $P(\theta|\sigma^{(0)})$  can be converted to a distribution  $P(K)$  for the probability of having a complementarity  $K$ . Up to a

normalization factor, it is given by

$$P(K) \propto \binom{N}{\frac{1}{2}(N+K)} \exp\left(\frac{\varepsilon\beta_D}{2} K\right). \quad (2)$$

Its first moment  $\langle K \rangle = \sum_K K P(K) = N \tanh(\varepsilon\beta_D/2)$  quantifies the quality of the design. For decreasing design temperatures  $1/\beta_D$  the average complementarity per site  $\langle K \rangle/N$  approaches one, and thus the designed probe molecules are well optimized with respect to the target.

In the second step the association of the probe molecules with the target and with a different rival molecule is compared. Introducing the quantity  $Q = \sum_i \sigma_i^{(0)} \sigma_i^{(1)}$  as a measure for the similarity between the recognition sites of the target and the rival molecules, the free energy difference per site can be expressed in the form  $\Delta F(Q)/N = -\frac{1}{2}\varepsilon \tanh\left(\frac{\varepsilon\beta_D}{2}\right) (1 - Q/N)$ .  $\Delta F/N$  is negative, if the rival and the target are different and  $Q$  is thus smaller than  $N$ . The probe molecule therefore binds preferentially to the target molecule, and thus the target is specifically recognized. The free energy difference increases with decreasing similarity parameter  $Q$ .

After this introductory analysis of a simple system, we turn to consider more complex models which allow to investigate the influence of different factors on the specific recognition between surfaces. We begin with studying the role of cooperativity.

Systematic mutagenesis experiments have revealed that cooperativity plays an important role in molecular recognition processes [15]. Cooperativity in biological processes basically means that the interaction strength of two residues depends on the interactions in their neighborhood. Physically, this can be caused by a physical rearrangement of amino acid side-chains or a readjustment of polar moments as a function of the local environment. In the simplified language of our model, cooperativity thus means that the quality of a contact depends on the quality of the neighbor contacts. This can be incorporated in the HP-model by the following extension:

$$\mathcal{H}(\sigma, \theta; S) = -\varepsilon \sum_{i=1}^N \frac{1 + S_i}{2} \sigma_i \theta_i - J \sum_{\langle ij \rangle} S_i S_j. \quad (3)$$

The second sum accounts for the cooperative interaction and runs over neighbor residue positions  $i$  and  $j$ . The interaction coefficient  $J$  is positive for cooperative interactions and negative for anti-cooperativity. For  $J > 0$ , the cooperative term rewards additional contacts in the vicinity of a good contact between two residues. This leads to a better optimization of the side-chains and thus the complementarity between the probe and the target molecule is improved. Cooperativity is therefore expected to enhance the quality of the design step compared to an interaction without cooperativity. Similarly, one expects an improved recognition specificity.

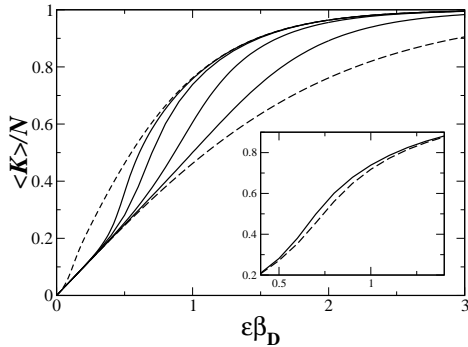


FIG. 1: Average complementarity per site of the designed probe ensemble for different values of  $J$ . For the lower dashed curve  $J = 0$ , the upper dashed line represents the limit  $J \rightarrow \infty$ , which can be tackled analytically [19]. The curves in between from bottom up belong to values 0.1, 0.25, 0.5, 0.75 of  $J$  in units of  $\varepsilon$ . The inset shows  $\langle K \rangle / N$  for  $N = 256$  (full curve) and  $N = 36$  (dashed line) with  $J = \varepsilon/2$ . Only minor finite-size effects are visible.

For non-zero, but finite values of  $J$ , the model can no longer be solved analytically. Therefore, we calculated numerically the density of states for the interaction between two proteins as a function of the energy and the complementarity parameter using efficient modern Monte Carlo algorithms [16, 17]. The density of states  $\Omega_J(K, E)$  for a fixed target structure  $\sigma^{(0)}$  is the number of configurations  $(\theta, S)$  that have energy  $E = \mathcal{H}$  when interacting with the target, and a complementarity  $K$  with the target recognition site. The probability distribution of the complementarity  $K$  is then (up to a normalization constant) given by  $P_{\beta_D}(K; J) \sim \sum_E \Omega_J(K, E) \exp(-\beta_D E)$ .

For simplicity, we consider asymptotically large interfaces on a square lattice. (The actual calculations shown here were carried out with  $N = 256$ , and we checked that the results do not change any more for larger  $N$ ). Fig. 1 shows the average complementarity  $\langle K \rangle / N$  for different cooperativities  $J$ . Cooperativity is found to increase the average complementarity of the designed probe molecules for large enough values of the parameter  $\varepsilon \beta_D$ . For  $\varepsilon \beta_D \sim 1$ , a small change in the cooperativity  $J$  leads to a large difference in the average complementarity, *i.e.*, small changes in  $J$  can have a large impact on the recognition process. As  $\varepsilon$  is typically of the order of 1 kcal/mole, this regime indeed corresponds to physiological conditions for reasonable design temperatures,  $1/\beta_D \lesssim 1/\beta_{\text{room}}$ . Fig. 2 shows the free energy difference per site  $\Delta F(Q)/N$  of the association of probe molecules with the target structure and a rival structure, for different values of the cooperativity constant  $J$ . Increasing the cooperativity increases the free energy difference. Relatively small cooperativities are sufficient to obtain an effect, and the maximum effect of cooperativity is already reached for a value  $J \simeq \varepsilon$ . Thus, we find that cooperativity indeed improves the recognition ability as

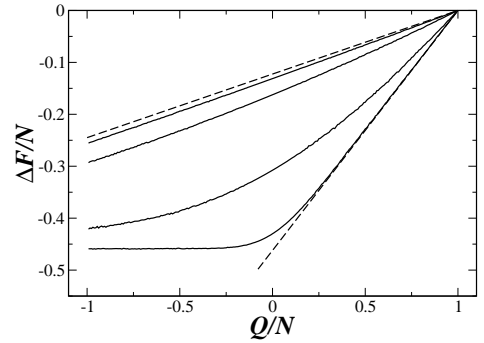


FIG. 2: Free energy difference per site (in arbitrary units) of the association of the probe ensemble with the two competing molecules as a function of their similarity for different cooperativities  $J$  (with  $\beta_D = \beta = 0.5$ ). For the upper dashed line  $J = 0$ , the lower dashed line describes the limiting case  $J \rightarrow \infty$  for  $Q/N$  close to one [19]. The full curves from top to bottom correspond to the same values of  $J$  as in Fig. 1.

expected for cooperativity constants  $J \simeq \varepsilon$ . The above findings were obtained for large interfaces. Although minor finite-size effects are visible for interfaces of realistic size (with  $N \sim \mathcal{O}(30)$ ) the general findings discussed above still hold qualitatively (compare inset of Fig. 1).

In situations where one molecule is flexible conformational changes occur. However, cooperativity works on the level of residue interactions and thus we expect that the favorable effect of cooperativity to molecular recognition is not spoiled by the entropic contributions due to refolding. This, however, needs further investigation. Note that flexible binding has been addressed recently [18].

Next, we investigate the role of the interplay of interactions for molecular recognition. This study is motivated by the observation that antibody-antigen interfaces have very specific properties. Mutagenesis studies have revealed that the structural interface in these complexes is different from the functional recognition site made up of those residues that contribute to the binding energy. Only approximately one quarter of the residues at the interface contribute considerably to the binding energy [10, 20]. These contributing residues are sometimes called “hot spots”. In addition it has been shown that antigen-antibody interfaces are less hydrophobic, compared to other protein-protein interfaces, so that the relatively strong hydrogen bonds are more important [10]. In the immune system molecular recognition must satisfy very specific requirements. The immune system has to recognize substances that have never been encountered before. Thus antigen-antibody recognition has to exhibit a large flexibility [9], and has to be able to adapt very rapidly by evolution. These peculiarities of antibody-antigen interfaces suggest that selective molecular interactions are obtained most efficiently with only a few strong interactions across the interface, so that a complementarity with the whole recognition site is not necessary.

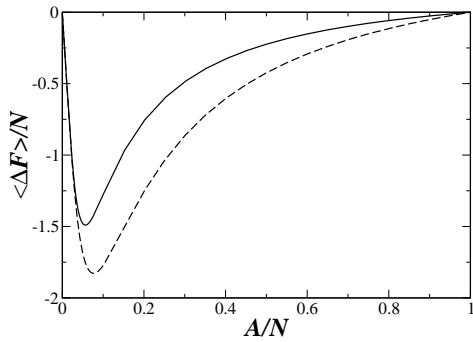


FIG. 3: Averaged free energy difference per site (in arbitrary units) as a function of the fraction  $A/N$  of active residues for  $\varepsilon_H A/N = 0.1$ . The full curve corresponds to a ratio  $\beta/\beta_D = 1$ , the dashed curve to  $\beta/\beta_D = 1/2$ .

Within our two-stage approach, we can address the question whether few but strong bonds or many but weak bonds are more favorable. To this end we consider a model which distinguishes between active and inactive residues only. Only active residues contribute to a bond. The variables  $\sigma$  and  $\theta$  now take on the values  $\sigma_i, \theta_i = +1$  for active and  $\sigma_i, \theta_i = 0$  for inactive residues, and the Hamiltonian is given by

$$\mathcal{H}(\sigma, \theta, S) = -\varepsilon_H \sum_{i=1}^N \frac{1 + S_i}{2} \sigma_i \theta_i \quad (4)$$

with  $S_i$  specifying again the quality of the contact of residues, and  $\varepsilon_H$  giving the interaction strength. Moreover, we extend the design step by fixing the average number of active residues  $A = \langle \sum_i \theta_i \rangle$  on the probe molecules with a Lagrange parameter. The total interaction energy  $E$  is also subject to restrictions: It has to exceed the thermal energy to stabilize the complex, but on the other hand it has to be small enough to ensure the high flexibility of the target-probe complex that is crucial for the immune system. When increasing the average number of active residues  $A$ , one must therefore reduce the interaction energy  $\varepsilon_H$  accordingly, *e.g.*, by keeping the product  $E \approx A\varepsilon_H$  constant.

Figure 3 shows as a function of  $A/N$  the average free energy difference per site  $\Delta F/N$  of the association with the target molecule and a rival molecule, averaged over all possible target and rival structures  $\sigma$ . We find that  $\langle \Delta F \rangle$  exhibits a minimum at a small fraction  $A/N$  of active residues. The position of the minimum at small fractions of  $A/N$  is fairly insensitive to a variation of the interaction parameters. Hence this simple coarse-grained model already predicts that molecular recognition is most efficient if the functional recognition site consists only of a small fraction of the structural recognition site, as is indeed observed in antibody-antigen complexes.

In conclusion, we have presented coarse-grained models which allow to study generic features of biomolecular

recognition. A two-stage approach which distinguishes between the design of probe molecules and the test of their recognition abilities has been adopted. We have applied the approach to investigate the role of cooperativity and of hydrogen bonding for molecular recognition. It turned out that cooperativity can substantially influence the efficiency of both design and recognition ability of recognition sites. Our model also reproduces the observation that the structural recognition site has to be distinguished from a functional recognition site in highly flexible complexes such as antigen-antibody complexes.

The approach can readily be generalized to study other aspects of molecular recognition. For example, it will be interesting to investigate the influence of the heterogeneity of the mixture of target and rival molecules in physiological situations. This can be incorporated by considering ensembles of targets and rivals differing in certain properties as for example correlations and length scales. A recent study indeed showed that the local small-scale structure of molecules seems to be important for molecular recognition [6].

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