# Influence of correlations on molecular recognition

Hans Behringer and Friederike Schmid
*Fakultät für Physik, Universität Bielefeld, D-33615 Bielefeld, Germany*
(Received 13 May 2008; published 3 September 2008)

The influence of the patchiness and correlations in the distribution of hydrophobic and polar residues at the interface between two rigid biomolecules on their recognition ability is investigated in idealized coarse-grained lattice models. A general two-stage approach is utilized where an ensemble of probe molecules is designed first and the recognition ability of the probe ensemble is related to the free energy of association with both the target molecule and a different rival molecule in a second step. The influence of correlation effects are investigated using numerical Monte Carlo techniques and mean field methods. Correlations lead to different optimum characteristic lengths of the hydrophobic and polar patches for the mutual design of the two biomolecules on the one hand and their recognition ability in the presence of other molecules on the other hand.

DOI: 10.1103/PhysRevE.78.031903 PACS number(s): 87.15.A−, 89.20.−a

## I. INTRODUCTION

An understanding of the basic principles of biomolecular recognition, that is the ability of a biomolecule to interact selectively 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 [1–3]. The recognition process itself is governed by a complex interplay of noncovalent interactions such as salt bridges, hydrogen bonds, van der Waals and hydrophobic interactions. The typical intrinsic energy contribution of such an interaction is of the order of 1–2 kcal/mol and is thus only slightly larger than the thermal energy $k_B T_{room}=0.62$ kcal/mol at room temperature [4,5]. In order to stabilize a complex of two proteins over a time long enough to ensure its biological function, many favorable interactions have to be established to overcome the entropic cost of the formation of the complex. Therefore, the two molecules have to complement each other at the common interface with respect to shape and interaction partners [6]. This principle of complementarity is closely related to the lock-and-key view of rigid protein-protein recognition [7].

Molecular recognition results from an interplay of numerous competing and cooperating factors. Apart from the scenario of recognition between rigid proteins, recognition processes where at least one of the biomolecules undergoes conformational changes are also numerous in nature. Such recognition processes are described by the induced fit scheme [8]. To understand the recognition process in full, one not only needs to consider the stability of a single specific complex, but also the encounter of the two biomolecules in the heterogeneous environment of the cell. For example, long-range electrostatic interactions are believed to preorient the biomolecules so that the probability of an encounter of the complementary patches on the two molecules upon collision is increased [2,9]. Another critical aspect is the competition due to the simultaneous presence of different molecules. The more the binding free energy between complementary biomolecules differ from the binding free energy to other molecules the lower is the risk of misrecognition.

The recognition problem of two biomolecules shows up in different disguises in nature. To gain insight into this problem different approaches can be adopted. A detailed modeling (often on an atomistic level) of the biomolecules that form a complex gives many insights into the actual binding process between two specific biomolecules. In drug design docking methods allow the identification of the drug molecule with the optimum binding affinity for a known biomolecule. A second way to investigate the problem of molecular recognition is the use of coarse-grained models. The study of idealized coarse-grained and hence abstract generic models with methods from statistical physics seems to be particularly adequate for an understanding of the basic common physical mechanisms that govern different recognition processes in the heterogeneous environment of a cell. The coarse-graining approach is based on a reduction to the most relevant degrees of freedom for molecular recognition which helps to abstract from complications due to the intricate interplay of the involved types of interactions so that the generic features nature exploits for recognition can be identified [10]. This approach has been adopted in the literature to analyze various aspects of biomolecular binding and recognition for (almost) rigid and flexible biomolecules in idealized model systems [11–19].

One popular approach to study the basic principles of molecular recognition consists in investigating the adsorption of heteropolymers on patterned surfaces. Biomolecular recognition is then viewed in a first approximation as the adsorption of a biopolymer on the surface of another biopolymer. One major aspect addressed in this context deals with the question, whether or not length scale matching on the two polymers favors adsorption [20–26]. Generally speaking it was found that the adsorption properties depend on the involved types of correlations and that statistically structured surfaces (be it correlated or anticorrelated ones) have an enhanced affinity towards similarly structured chains although an exact matching of the corresponding correlation lengths is not necessary. The adsorption is followed by a second freezing transition where the flexible chain adjusts to the pattern of the surface which necessitates a more precise matching of the correlation lengths. Bogner *et al.* [16] also addressed the role of correlations and found that biomolecular binding seems to be strongly influenced by small scale structures suggesting

 

that local structure elements are particularly important for molecular recognition.

The present study is in some sense complementary to those works. We investigate the influence of correlation effects on molecular recognition within coarse-grained models that are specifically designed to model the recognition between almost rigid proteins. In particular we focus on the role of the presence of competing rival molecules on the recognition characteristics. In our model correlations appear in the distribution of hydrophobic and polar residues on the surface of a biomolecule. These correlations result in extended patches of several hydrophobic and polar residues on the surface of the protein. The patterns of the actual target molecule and the rival molecules thereby exhibit the same characteristic correlation lengths. We then address the question about the optimum correlation length of the biomolecule that is supposed to recognize the target. All in all our analysis shows that a matching of the patterns on the surfaces is necessary to a certain degree in order to obtain optimum selectivity. However, the precise way how the correlation lengths fit to each other depends on whether or not rival molecules are present, that is whether the isolated binding process or whether the actual recognition process with rival molecules present is considered. We note also that in a recent study the effect of correlations that stem from the density of atoms on the surface of a biomolecule was considered in the context of connected proteins in protein interaction networks [27].

The present article is organized in the following way. In the next section our general approach to biomolecular recognition of two rigid proteins in the presence of rival molecules is briefly sketched (for a more detailed account, see [28,29]). In the subsequent Sec. III we discuss how correlations in the distribution of hydrophobic and polar residues can be incorporated into the model. In Secs. IV and V we then investigate the influence of sequence correlations on molecular recognition by using Monte Carlo techniques and mean field approximations.

## II. MODEL AND GENERAL APPROACH TO MOLECULAR RECOGNITION

In this work we use coarse-grained idealized model systems to investigate the recognition of two biomolecules. Coarse-grained model systems contain a limited number of degrees of freedom and hence the recognition problem in its various disguises cannot be captured in its full scope. We limit our investigations to recognition processes that belong to the scenario of rigid protein-protein recognition and consider only the stabilization of the complex. Dynamical aspects concerning the encounter of the two proteins in the cell and the formation of the complex are not incorporated. The generic model we use is built on observations of (universal) features of rigid protein-protein recognition so that the physics which different recognition processes have in common is captured in the model.

We apply a coarse-grained point of view on the level of both the sequence of the amino acids on the so-called recognition sites of biomolecules at the mutual interface and the residue-residue interactions stabilizing the complex. The backbones of the proteins 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 [2,3,30]. Motivated by the observation that hydrophobicity is the major driving force in molecular recognition [2,9,30,31] we describe the type of the residue at the position $i=1,\ldots,N$ of the recognition site by a binary variable [28,29] where one of the two values represents a hydrophobic residue and the other one a polar residue. Note, that an eigenvalue decomposition of the Miyazawa-Jernigan matrix leads to an approximate parametrization of residue-residue interactions by an Ising-like energy term with discrete variables that can take on two distinct values [32]. This gives additional justification to the use of hydrophobic-polar (HP) models for the residue-residue interactions. Denoting the type of the residue at position $i$ of the recognition site of one of the two molecules by $\sigma_i \in \{+1(\text{hydrophobic}), -1(\text{polar})\}$ the residue sequence on the recognition site with $N$ residues is then specified by $\sigma = (\sigma_1, \ldots, \sigma_N)$. Similarly the type of residue at position $i$ of the recognition site of the interaction partner is specified by $\theta = (\theta_1, \ldots, \theta_N)$ with $\theta_i \in \{\pm 1\}$.

We then model the energetics at the two-dimensional contact interface of the two biomolecules by

$$\mathcal{H}_{\text{int}}(\sigma, \theta; S) = -\varepsilon \sum_{i=1}^{N} \frac{1+S_i}{2} \sigma_i \theta_i - J \sum_{\langle i,j \rangle} S_i S_j, \qquad (1)$$

where the energy contributions of the contact between two residues across the interface are summed up. The variable $S_i$ takes on the two discrete values $\pm 1$ and describes the fit of the shape of the molecules at position $i$ of the interface, for a poor fit, i.e., $S_i=-1$, we assume no contribution to the stabilizing energy. The variable $S$ models the influence of a (local) rearrangement of the amino acid side chains on a microscopic level when the complex is formed [2,9,30]. Note that such rearrangements are observed even if the tertiary structures of the proteins remain unaltered upon complex formation. Apart from the direct contact energy with strength $\varepsilon$ the model Hamiltonian (1) contains an additional cooperative interaction term where the quality of a residue-residue contact couples to the structure in its neighborhood. This term has the effect that a locally good fit at some position in the interface influences its neighborhood [29].

In our idealized view of the interface each biomolecule contributes with the same number $N$ of coarse-grained "residues." This assumption is questionable for real interfaces, particularly for curved interfaces different numbers of amino acids appear [9]. In Hamiltonian (1) a residue of one of the biomolecules interacts precisely with one residue on the other molecule. This simplified assumption is also not valid for real residues, in particular as different amino acids are of different sizes so that a large residue can interact with several smaller amino acids. However, one can think of a general partition of the interface in $N$ contact patches of the same size on each of the biomolecules where larger amino acids contribute to several patches whereas small ones only to a few. A value of the hydrophobicity can then be attributed to each of the patches on the biomolecules. Within such a de-

scription the (free) energies can be approximated by the model (1). For the sake of simplicity, however, we stick to the expression "residue" in the following discussions. We also note that solvation effects at the recognition sites and the associated entropy changes are crucial when the complex of two biomolecules is formed [33,34]. In the adopted coarse-grained approach, however, it is assumed that all these contributions are of comparable size for all proteins under consideration. Notice also that by reducing the interactions to the hydrophobic effect solvation effects are already partially included in HP-like models [on a formal level due to integrating out the solvent degrees of freedom resulting in effective interaction constants such as $\varepsilon$ in Eq. (1)].

To study the recognition process between two rigid proteins we adopt a two-stage approach. For a fixed target sequence $\sigma^{(t)}$ we first design an ensemble of probe molecules $\theta$ at a design temperature $1/\beta_D$ in such a way that the sequence $\theta$ should optimize the interface energy. This design by equilibration leads to the distribution $P(\theta|\sigma^{(t)}) = \frac{1}{Z_D}\Sigma_S \exp(-\beta_D \mathcal{H}(\sigma^{(t)}, \theta; S))$. This first step should mimic evolutionary processes or the design of artificial molecules in biotechnological applications. The quality of the design can be quantified by evaluating the average $\langle K\rangle_{P(\theta|\sigma^{(t)})}$ of the overlap $K=\Sigma_i \sigma_i^{(t)}\theta_i$ of the sequence of the probe molecules with the previously fixed target sequence. A large $\langle K\rangle_{P(\theta|\sigma^{(t)})}$ then signals a high complementarity of the two recognition sites in regard to the actual recognition process of the two proteins. Notice that $\langle K\rangle_{P(\theta|\sigma^{(t)})}$ is generally dependent on the particular chosen target sequence $\sigma^{(t)}$.

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 $\sigma^{(t)}$ on the one hand and a structurally different rival molecule $\sigma^{(r)}$ on the other hand. In this step the free energy of the interaction

$$F(\theta|\sigma^{(\alpha)}) = -\frac{1}{\beta}\ln\left(\sum_S \exp(-\beta\mathcal{H}(\sigma^{(\alpha)}, \theta; S))\right) \tag{2}$$

of the molecule $\sigma^{(\alpha)}$, $\alpha \in \{\text{t(target)}, \text{r(rival)}\}$, with a particular probe sequence $\theta$ has to be averaged with respect to the distribution $P(\theta|\sigma^{(t)})$ giving $F^{(\alpha)}=\langle F(\theta|\sigma^{(\alpha)})\rangle_{P(\theta|\sigma^{(t)})}$. This leads finally to the free energy difference $\Delta F(\sigma^{(t)}, \sigma^{(r)}) = F^{(t)} - F^{(r)}$. In order to value the recognition ability of the system the free energy difference $\Delta F$ is then averaged over all possible target and rival sequences on their respective recognition sites,

$$[\Delta F]_{\sigma^{(t)},\sigma^{(r)}} = \sum_{\sigma^{(t)},\sigma^{(r)}} W^{(t)}(\sigma^{(t)}) W^{(r)}(\sigma^{(r)}) \Delta F, \tag{3}$$

where the $W^{(\alpha)}$ denote the distributions of the sequence of the target and rival molecules, respectively. A negative $[\Delta F]_{\sigma^{(t)},\sigma^{(r)}}$ then signals an overall preferential interaction of the probe molecule with the target leading to the desired selectivity of the recognition process. In the following discussions square brackets indicate an average over all possible target and rival sequences whereas pointed brackets denote an average over the designed ensemble of probe molecules.

Our approach can be roughly illustrated by the technologically relevant case of developing a drug molecule with a high affinity to a particular protein. The target molecule of our terminology corresponds to a known protein which is responsible for a disease, for example, with a well-located recognition site. Our design step then corresponds to finding the most suitable drug molecule called probe in our nomenclature. The subsequent testing step then models the administration of the drug to an organism where additional proteins (rival molecules) are present apart from the known protein the drug molecule is supposed to bind to, so that all these proteins can compete for the drug molecules.

## III. INCORPORATING SEQUENCE CORRELATIONS

In Hamiltonian (1) only the energetics of the contact interactions of residues across the interface between the two interacting molecules is taken into account. However, the residues that constitute the recognition sites on the proteins also interact with each other, so that different sequences result in different contributions to the total energy. Noncovalent hydrophobic-polar contacts between neighboring residues in the recognition sites, for example, lead to unfavorable energy contributions. As a consequence patches of several hydrophobic or polar residues are likely to show up. Thus the probability of having a certain type of residue at position $i$, say, in the recognition site depends on the type of the residues in the neighborhood of $i$, so that the sequences are correlated. Indeed the appearance of patches of residues of a similar hydrophobicity can be observed in the majority of protein-protein interfaces [35].

On a formal level, correlations can be incorporated by introducing, apart from the contact energy $\mathcal{H}_{int}$ at the interface, an additional correlation term $\mathcal{H}_{cor}$ to the Hamiltonian. Note that in principle correlation energies also show up in the interior of the proteins and in turn induce correlations on the surface of the molecules. In this work, however, we are only concerned with the interaction between two proteins which depends on the nature of the residues that constitute the recognition sites. We thus do not consider these further distributions of interior (or other surface) residues explicitly.

Focusing on the sequence $\theta$ of the probe molecules for the discussion we consider the following correlation energy:

$$\mathcal{H}_{cor} = -\gamma_p \sum_{\langle i,j\rangle} \theta_i\theta_j - \mu_p \sum_i \theta_i. \tag{4}$$

The first sum extends over all neighboring residues in contact and hence represents the interactions due to hydrophobicity so that the associated parameter $\gamma_p$ thus controls the corresponding (nearest-neighbor) correlations. These correlation interactions lead to the formation of extended patches of either hydrophobic or polar residues in the recognition sites. The characteristic extensions of these patches can be interpreted as a measure of the correlation length $\lambda_p$. In the second contribution the hydrophobicity of the recognition site couples to the parameter $\mu_p$ which therefore controls the overall number of hydrophobic residues. The design step then gives the probability of a certain probe sequence $\theta$ for a given target sequence $\sigma^{(t)}$. This probability distribution for the probe ensemble is then generally given by

$$P(\theta|\sigma^{(t)}) = \frac{1}{\mathcal{N}} \exp(-\beta_D \mathcal{H}_{int} - \mathcal{H}_{cor}) \quad (5)$$

where $\mathcal{N}$ denotes the normalization. In general this probability depends on the particular sequence $\sigma^{(t)}$ of the recognition site of the given target. Note that the contributions from the correlation energy are considered not to be subjected to thermal fluctuations as only the rearrangement variable $S$ is assumed to equilibrate.

After the average over the probe ensemble has been carried out the free energy difference $\Delta F(\sigma^{(t)}, \sigma^{(r)})$ for a given target-rival pair depends on the parameters $\gamma_p$ and $\mu_p$. For the final average over the possible target and rival molecules sequences with particular correlation properties are considered. Formally the corresponding probability distributions for $\alpha \in \{t(target), r(rival)\}$ are given by

$$W^{(\alpha)}(\sigma^{(\alpha)}) \sim \exp(-\mathcal{H}_{cor}(\sigma^{(\alpha)})) \quad (6)$$

with associated parameters $\gamma_\alpha$ for the (nearest-neighbour) correlations and $\mu_\alpha$ for the overall hydrophobicity

$$H_\alpha = Nh_\alpha = \left[\sum_i \sigma_i^{(\alpha)}\right]_{W^{(\alpha)}}. \quad (7)$$

For the investigation of the influence of sequence correlations on molecular recognition in our model we adopted the following strategy. For a fixed pair of target and rival sequences the probe ensemble will be generated for the parameters $\gamma_p$ and $\mu_p$, which in turn determine the correlation length $\lambda_p$. Note that the generated probe molecules are not perfect with respect to the target molecule due to evolutionary processes leading to defects. Then the recognition ability is assessed by evaluating the free energy difference $\Delta F(\sigma^{(t)}, \sigma^{(r)})$ for the given target-rival pair. This free energy difference is then averaged over all possible target-rival pairs, where similarly to the probe molecule the associated parameters $\gamma_\alpha$ and $\mu_\alpha$ determine the correlation lengths $\lambda_\alpha$. By this approach the overall recognition ability $[\Delta F]_{\sigma^{(t)},\sigma^{(r)}}(\lambda_t, \lambda_r, \lambda_p)$ is hence computed as a function of the correlation lengths (and hydrophobicities) of the target and rival molecules and of the predesigned probe molecules. For given correlation lengths $\lambda_t$ and $\lambda_r$ of the target and rival molecules, respectively, the correlation length $\lambda_p$ of the probe molecules is then varied to find the optimum recognition ability.

## IV. UNCOOPERATIVE MODEL

The interaction energy (1) at the interface between the two proteins comprises apart form the direct contact contributions due to hydrophobicity additional cooperative terms where the rearrangements of neighboring amino acid side chains couple to each other. In this section we set the corresponding interaction constant $J$ to zero and consider only the direct hydrophobic energy contributions. The total Hamiltonian for the interface energy between a molecule with the sequence $\sigma$ and the probe molecule $\theta$ thus reads

$$\mathcal{H}(\sigma, \theta; S) = \mathcal{H}_{int} + \frac{1}{\beta}\mathcal{H}_{corr} = -\varepsilon \sum_{i=1}^{N} \frac{1+S_i}{2}\sigma_i\theta_i - \frac{\gamma_p}{\beta}\sum_{\langle i,j\rangle}\theta_i\theta_j - \frac{\mu_p}{\beta}\sum_i \theta_i. \quad (8)$$

As the interaction variable $S_i$ at position $i$ does not couple to the variables at other positions $j \neq i$ of the interface the corresponding thermal average can be carried out resulting in an effective Hamiltonian that depends only on the sequence variables any more. Including the contributions from the correlation energies it is given by

$$\mathcal{H}_{eff}(\sigma, \theta) = -\frac{\varepsilon}{2}\sum_i \sigma_i\theta_i - \frac{\gamma_p}{\beta}\sum_{\langle i,j\rangle}\theta_i\theta_j - \frac{\mu_p}{\beta}\sum_i \theta_i + \text{const.} \quad (9)$$

Here we have used the fact that $\cosh(\beta\varepsilon\sigma_i\theta_i) = \cosh(\beta\varepsilon)$ for all choices of $\sigma_i$ and $\theta_i$. The constant in Eq. (9) is temperature dependent, however, as we are only concerned with the effect of correlations on the molecular recognition ability, we fix the temperature and thus can omit the constant. The free energy for the interaction between the sequences $\sigma$ and $\theta$ is $F(\theta|\sigma) = -\frac{\varepsilon}{2}\Sigma_i\sigma_i\theta_i + \frac{1}{\beta}\mathcal{H}_{cor}(\theta)$ and can now be averaged over the possible probe sequences that are distributed according to the probability $P(\theta|\sigma^{(t)}) \sim \exp(-\beta\mathcal{H}_{eff}(\sigma^{(t)}, \theta))$. Note that the design might be carried out at a temperature $\beta_D$ which is different from the temperature $\beta$ at which the selectivity is determined. However, we are not interested in the effect of a temperature variation in this work and therefore choose $\beta_D = \beta$. The correlation energy $\mathcal{H}_{cor}$ does not explicitly depend on the sequence $\sigma^{(\alpha)}$ and hence when computing the free energy difference between the interaction of the target molecule with the probe ensemble on the one hand and the interaction of the rival molecule with the probe ensemble on the other hand these correlation contributions cancel and one ends up with

$$\Delta F(\sigma^{(t)}, \sigma^{(r)}) = -\frac{\varepsilon}{2}\sum_i (\sigma_i^{(t)} - \sigma_i^{(r)})\langle\theta_i\rangle_{P(\theta|\sigma^{(t)})}. \quad (10)$$

The free energy difference is hence determined by the difference of the complementarity of the probe ensemble with the target sequence on the one hand and the complementarity of the probe ensemble with the rival sequence on the other hand. Note also that the free energy difference exhibits a dependence on the correlation parameters $\gamma_p$ and $\mu_p$ (which enter the distribution $P$ and hence influence the average hydrophobicity at position $i$ of the recognition site of the probe molecule) and thus on the correlation length $\lambda_p$.

To assess the overall recognition ability the free energy difference (10) has to be averaged over all target and rival sequences which are distributed with respect to Eq. (6) with correlation Hamiltonians of the form (4). As the target and the rival sequences are independent of each other, the averaged free energy difference is therefore given by

$$[\Delta F] = -\frac{\varepsilon}{2}\sum_i [\sigma_i^{(t)}\langle\theta_i\rangle_{P(\theta|\sigma^{(t)})}]_{W^{(t)}} + \frac{\varepsilon}{2}N[h_p]_{W^{(t)}}h_r \quad (11)$$

$$= -\frac{\varepsilon}{2}[\langle K\rangle_{P(\theta|\sigma^{(t)})}]_{W^{(t)}} + \frac{\varepsilon}{2}N[h_p]_{W^{(t)}}h_r \quad (12)$$

in terms of the complementarity of the probe ensemble and hydrophobicities $h_p$ and $h_r$ of the probe and rival molecule, respectively. The second term originates from the interaction of the probe molecules with the rival molecule. It is only determined by the respective hydrophobicities of the molecules and is independent of the structure elements related to the hydrophobic and polar patches of the recognition sites. Note that the hydrophobicity $h_p$ hinges on the sequence of the target molecule. The first term stems from interactions of the probe molecule with the target molecule. This term depends sensitively on an appropriate matching of the structure elements on the recognition sites and is hence directly influenced by correlation effects in the corresponding distributions of the hydrophobicity.

In the following sections we use two methods to carry out the remaining averages in Eq. (12), namely numerical Monte Carlo techniques and a mean field approximation. Larsen *et al.* reported that basically two types of interfaces appear in protein-protein complexes [35]. In the minority of complexes the interface has a hydrophobic core which consists of a single large patch and which is surrounded by a rim of polar interactions with residual accessibility by solvent molecules. For the majority of complexes, however, the interface is made up by a mixture of small hydrophobic patches and polar interactions. We thus focus in the following discussions only on the situation where the correlation lengths of the target and rival molecule, respectively, are relatively small compared to the extension of the interface.

### A. Numerical results

The remaining averages in expression (12) of the free energy difference—first over the probe ensemble with the distribution $P(\theta|\sigma^{(t)})$ and then over the target sequences with the distribution $W^{(t)}$—can be carried out numerically by means of Monte Carlo methods. For a given target and rival sequence the quantities of interest (averaged complementarity and free energy difference as a measure for selectivity) are computed first. Then the final average over the target sequences with fixed parameters $\gamma_t$ and $\mu_t$ (and hence fixed correlation length $\lambda_t$ and hydrophobicity $h_t$) is evaluated. As we are interested in the recognition ability of the system if the rival molecule is structurally very similar to the target molecule, the same correlation parameters are used for the average over the rival sequences and thus one has in particular $h_r = h_t$.

The probe molecules are designed for different correlation parameters $\gamma_p$. The probe sequence is optimized with respect to the target sequence, thus we do not further restrict the hydrophobicity and therefore set $\mu_p = 0$. The correlation parameter $\gamma_p$ can therefore be directly converted into the correlation length $\lambda_p$. The (pseudo) correlation length for recognition sites of a finite extension is computed to be the average size of clusters that are made up of neighboring residues of the same type. In the following figures the shown correlation length $\lambda_p$ is normalized in such a way that its maximum possible value is one for a system where the whole recognition site is made up of precisely one cluster with either hydrophobic or polar residues.

Alternatively the correlation length of a finite system can be defined by the second moment of an (appropriately normalized) correlation function [36]. However, both definitions lead to the same qualitative behavior of the correlation length as a function of the varying correlation parameters. The correlation length increases monotonically as a function of the correlation parameter $\gamma_p$ and saturates for sufficiently large values. Note also that in [37] the correlations on a finite surface where measured by a so-called patchiness which was defined to be basically the (suitably normalized) expectation value of the correlation energy $\Sigma_{\langle ij\rangle}\theta_i\theta_j$ in terms of our notation and convention.

For simplicity the systems considered for the Monte Carlo simulations are of regular rectangular geometry and contain between 64 and 256 spin variables. Note that real recognition sites contain typically 30–40 residues, however, up to minor finite-size effects we find the same qualitative behavior for systems of different sizes. As indicated in the introduction the energy contribution $\varepsilon$ of a non-covalent bond is only slightly stronger than the thermal energy at physiological conditions. We therefore typically choose $\beta\varepsilon \geqslant O(1)$. In the following results we discuss the system with $\beta\varepsilon = 1$ if not stated otherwise.

Consider a system with targets and rivals whose correlation length is relatively small so that the recognition sites consist of a relatively large number of rather small hydrophobic and polar patches. We investigated systems with hydrophobicities ranging from $h_{t/r} = 0.0$ to $h_{t/r} = 0.5$ and correlation lengths between $\lambda_{t/r} = 0.2$ and $\lambda_{t/r} = 0.35$ (note that the uncorrelated system with $\gamma_{t/r} = 0.0$ corresponds to a correlation length larger than the minimum length $\lambda_{t/r} = 1/L$ for a system with linear extension $L$ due to finite size effects). For all the systems we find the same qualitative behavior, we therefore discuss exemplarily the system with $L = 16$ and $\lambda_{t/r} = 0.263$ in the following.

In Fig. 1 the average complementarity of the designed probe molecules is shown as a function of varying correlation length $\lambda_p$ of the recognition site of the probe molecules for different hydrophobicities of the target molecules. It has to be noted first, that the complementarity (as well as the selectivity, which is discussed below) is first enhanced by increasing correlations, reaches an optimum and finally decreases again. The probe molecules are expected to have a maximum complementarity if the patches of hydrophobic and polar residues on the target are matched by corresponding patches on the probe. However, the optimization of the probe ensemble is carried out at a finite temperature and therefore thermal fluctuations limit the complementarity due to defects in the distribution of the interaction partner as the patches fray out at their boundaries. The position of the maximum of the average complementarity, that corresponds to the optimum choice of the correlation length of the probe molecules, is shifted to slightly larger values compared to the fixed correlation length of the target molecule. This signals

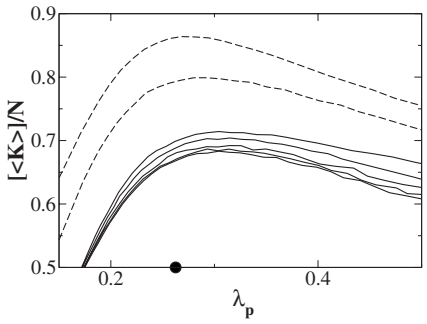


FIG. 1. Average complementarity of the probe ensemble with $\beta\varepsilon=1$ as a function of the correlation length for targets with different hydrophobicities (solid lines, from top to bottom, $h_t=0.5$, 0.4, 0.3, 0.2, and 0.1, the curve for $h_t=0.0$ is not shown as it is hardly distinguishable from the one with $h_t=0.1$ in the displayed range of $\lambda_p$). The correlation length of the targets is fixed to the value indicated by the black circle ($\lambda_t=0.263$, corresponding, e.g., to $\gamma_t=0.4$ for $h_t=0.0$). The optimum of the complementarity is slightly shifted to larger correlation lengths on the probe molecule. For the dashed curves $\beta\varepsilon=1.5$ and 2.0 (from the bottom up), again with $h_t=0.5$.

the fact that a slightly larger correlation length compensates the appearance of defects in the boundaries of the patches during the design step and thus increases the complementarity. This effect is less pronounced if the temperature is decreased as defects appear more seldom. Notice also that the average complementarity tends to the fixed hydrophobicity $h_t$ of the target in the limit $\lambda_p \to 1$ as in this case the recognition site of the probe is made up of hydrophobic residues only (compare Fig. 2).

For the uncooperative model (1) of the direct contact energy at the interface between the biomolecules the free energy difference is determined by the difference in the

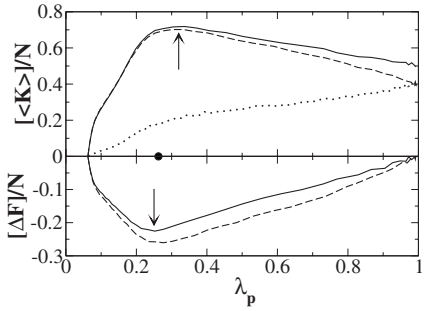


FIG. 2. The complementarity $[\langle K\rangle]/N$ and the free energy difference $[\Delta F]/N$ as a function of the correlation length of the probe molecules. The correlation lengths of the target and rival molecules are fixed to the value shown by the circle ($\lambda_t=\lambda_r=0.263$), the corresponding hydrophobicities are $h_t=h_r=0.5$ (solid line) and 0.4 (dashed line). Compared to the optimum for the design of the probe molecules, the optimum of the recognition ability is clearly shifted to smaller values of the correlation length on the probe molecule (optima indicated by arrows for $h_t=0.5$). Additionally, the complementarity of the probe ensemble with respect to the rival molecules is shown for $h_t=0.4$ (dotted line). Notice that the system for the shown data has a linear extension $L=16$ and hence the minimum possible correlation length is $\lambda_p \approx 0.06$, the uncorrelated system with $\gamma_p=0$ has $\lambda_p \approx 0.16$.

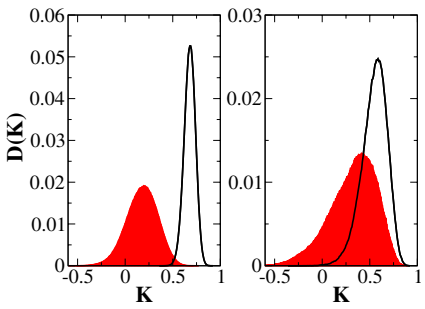


FIG. 3. (Color online) Distribution of the complementarity of the probe ensemble with respect to the target molecules (solid line) and the rival molecules (shaded curve) for different correlation lengths on the recognition site of the probe molecules. On the left hand side the correlation length $\lambda_p=0.25$, on the right-hand side $\lambda_p=0.75$. The hydrophobicities of the target and rival molecules are $h_t=h_r=0.4$, the correlation lengths are $\lambda_t=\lambda_r=0.263$ in each case.

complementarity of the probe ensemble with respect to the target molecules and the rival molecules, respectively [compare relation (10)]. In Fig. 2 (upper part) the complementarity with the rival molecules is shown in comparison with the one with respect to the target as a function of the correlation length $\lambda_p$. The probe ensemble is always more complementary to the target, with respect to which it has been optimized during the design step. For an increasing correlation length on the probe molecule the complementarity with respect to the rival sequence is increased until it finally reaches the maximum possible value for $\lambda_p \to 1$. In this case the probe is not structured any more and hence cannot discriminate between different sequences any more. In Fig. 3 the distribution $D(K)$ of the complementarity parameter with respect to the target and with respect to the rival molecules (averaged over all target and rival sequences) are compared for two different correlation lengths. For probe molecules with small structure elements with a characteristic length in the proximity of the optimum value the two distributions are well separated and hence the probe can discriminate the two molecules. For increasing correlation length and hence diminishing structuring of the probe molecules the two distributions approach each other and therefore selectivity is decreased. This comes along with a broadening of the distributions when going away from correlation lengths that correspond to the optimum conditions for the selectivity. For $\lambda_p \to 1$ to two distributions become eventually identical. Similarly, the two distributions are converging towards each other when the correlation length is decreased to the minimum possible value.

Figure 2 shows the free energy difference of the interaction of the probe molecules in a system with target and rival molecules, again as a function of the correlation length of the probe molecules. Note that the hydrophobicity $h_p$ in Eq. (12) exhibits a dependence on $\lambda_p$. For $\lambda_p \to 1$ the free energy difference has to vanish as the probe molecule consists only of amino acids of the same class in this case and hence it cannot distinguish on average between different sequences any more. The minimum of the free energy difference corresponds to a system with optimum recognition ability. The numerical results show that for recognition sites of the target

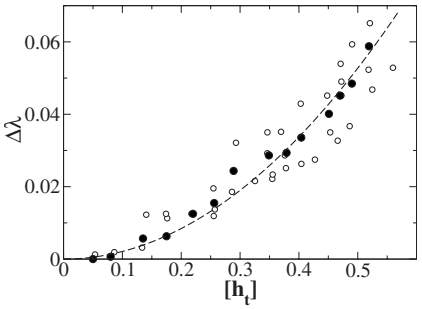


FIG. 4. The shift of the optimum value of the correlation length for the recognition ability compared to the optimum value for the complementarity as a function of the hydrophobicity of the target (note that $h_t=h_r$). Instead of error bars some of the results from the Monte Carlo runs (open circles) are shown together with the results of the analysis of the data (full circles). The dashed curve is a quadratic fit to the data (see discussion in Sec. IV B).

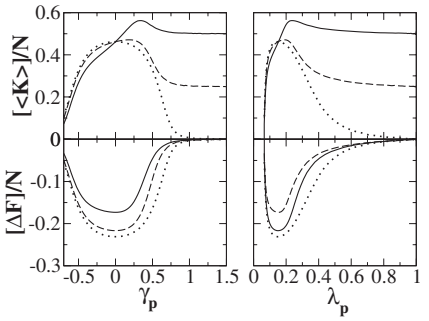


FIG. 5. The complementarity $[\langle K\rangle]/N$ and the free energy difference $[\Delta F]/N$ as a function of the correlation parameter $\gamma_p$ and of the correlation length $\lambda_p$, respectively, of the probe molecules. The correlation parameters of the target and rival molecules are set to zero, the corresponding hydrophobicities are fixed to the values $h_r=h_t=0.5$ (solid curve), 0.25 (dashed line), and 0.0 (dotted line). The free energy difference has an optimum for the correlation parameter $\gamma_p=0.0$, the optimum complementarity, however, is shifted to larger values.

with an excess of hydrophobic residues the optimum of the recognition ability is clearly shifted to smaller values of the correlation length compared to the appearance of the optimum in the design of the probe molecules. The reason for this shift lies in the fact that the structure elements of the recognition sites influence the contributions of the target-probe interactions to the free energy difference whereas the rival-probe interactions do not feel these structure elements. A smaller correlation length implies the appearance of an increased number of smaller patches on the recognition site of the probe molecule and hence an entropic benefit for the interaction with the target due to more possible ways to align each other favorably. This effect does not contribute to the free energy for the rival-probe interactions as it is insensitive to a matching of structure elements [compare relation (12) and the discussion there]. The emergence of the shift of the optimum correlation length also means that the design of the probe molecules has not to be carried out as effectively as one might expect naively. Therefore the system is at liberty to carry out the design not at the possible optimum way without losing the optimum recognition ability.

Interestingly this shift of the optimum correlation length depends on the value of the hydrophobicity of the target and rival molecule. Figure 4 shows that the shift vanishes for recognition sites with the same number of hydrophobic and polar residues [as is clear from relation (12)] and increases with increasing hydrophobicity. Note that in nature recognition sites with different hydrophobicities show up for proteins with different biological function. In enzyme-inhibitor complexes one typically finds largely hydrophobic interfaces whereas the hydrophobicity in antibody-antigen interfaces is significantly lowered [9,30].

Although the recognition sites in real systems show always extended patches of either hydrophobic or polar amino acids [35] we briefly discuss systems where no nearest-neighbor correlations appear in the distribution of the residues on the target and rival molecule. As a consequence the recognition site is rather diffuse on average concerning the distribution of hydrophobic and polar residues. The hydrophobicity of the corresponding recognition sites is nevertheless fixed to a certain value and the correlation length due to nearest-neighbor correlations is varied on the recognition site of the probe molecules to find the optimum selectivity. The results for different hydrophobicities are depicted in Fig. 5. The correlation parameter at which the optimum complementarity of the probe molecules with respect to the target molecules shows up depends on the hydrophobicity of the target and is shifted to values larger than zero for positive hydrophobicities. In this case the probe molecules prefer a correlated, i.e., patch-structured surface although the target surface is uncorrelated and thus unstructured. The free energy, on the other hand, has always its optimum for uncorrelated probe molecules. So again the design need not be carried out in the optimal way, but correlations will not enhance selectivity as in the case of correlated targets and rivals.

Finally we compare our results to the findings of the work by Lukatsky and Shakhnovich who investigated the influence of correlated density distributions at the interface between biomolecules [27]. From their study they deduced that the presence of correlations is a basic principle for recognition between proteins and lead to an enhanced probability to find such interfaces as hub-hub interactions in protein-protein networks. In our work we consider correlations in the distribution of hydrophobic and polar residues within the surface of the biomolecules. We basically reach the same conclusions as Lukatsky and Shakhnovich. The corresponding correlations lead to lower binding energies for moderately correlated interfaces as is indicated by the increase of the averaged complementarity as shown in Figs. 1 and 2. This points to a universal importance of (different) correlation effects to ensure the necessary specificity of recognition processes. Our approach contains an additional design step where the two recognizing proteins are optimized with respect to each other. Note that the expression "design" has been used in [27] to refer to the emergence of correlations.

### B. Mean field approximation

The averages in expression (12) of the free energy difference cannot be evaluated analytically, however, progress can

be made by applying a mean field approximation. Introducing the variable $k_i = \frac{\mu_p}{\beta} + \frac{\varepsilon}{2}\sigma_i^{(t)}$ the effective Hamiltonian that describes the distribution of the sequence of the probe molecules after the design step has been carried out is given by

$$\mathcal{H}_{\text{eff}}(\sigma^{(t)}, \theta) = -\frac{\gamma_p}{\beta}\sum_{\langle i,j\rangle}\theta_i\theta_j - \sum_i k_i\theta_i, \tag{13}$$

dropping an irrelevant temperature-dependent constant. The variable $k_i$ can be interpreted as a random variable whose probability is determined by the distribution $W^{(t)}$ of the target sequence. The system can therefore be viewed as a random field Ising model. The mean field treatment in the form of the equivalent neighbor approximation amounts to replacing $\mathcal{H}_{\text{eff}}$ by

$$\mathcal{H}_{\text{eff}}^{(\text{MF})}(\sigma^{(t)}, \theta) = -\frac{\gamma_p}{2N\beta}\left(\sum_i \theta_i\right)^2 - \sum_i k_i\theta_i. \tag{14}$$

The expectation value $\langle\theta_i\rangle_{P(\theta|\sigma^{(t)})}$ in Eq. (11) is then given by the derivative

$$\langle\theta_i\rangle_{P(\theta|\sigma^{(t)})} = -\frac{1}{N}\frac{\partial}{\partial k_i}G_{\text{eff}} \tag{15}$$

where the effective free energy $G_{\text{eff}}$ is related to the Hamiltonian $\mathcal{H}_{\text{eff}}^{(\text{MF})}$ by

$$G_{\text{eff}} = -\frac{1}{\beta}\ln Z_{\text{eff}} \tag{16}$$

with $Z_{\text{eff}} = \Sigma_\theta \exp(-\beta\mathcal{H}_{\text{eff}}^{(\text{MF})})$. The effective partition function $Z_{\text{eff}}$ can be calculated in the large $N$ limit by first using the identity

$$\exp\left(\frac{a}{2N}x^2\right) = \int_{-\infty}^{+\infty} dy \sqrt{\frac{Na}{2\pi}}\exp\left(-\frac{Na}{2}y^2 + axy\right) \tag{17}$$

(with $a > 0$), so that the variable $x := \Sigma_i\theta_i$ appearing quadratically in the Boltzmann factor of $Z_{\text{eff}}$ is linearized and hence the summation over $\theta$ can be carried out. The price to pay for this linearization is the introduction of the auxiliary variable $y$. Omitting irrelevant prefactors the effective partition function is then given by

$$Z_{\text{eff}} \sim \int_{-\infty}^{+\infty} dy \exp(N\mathcal{A}(y,k)) \tag{18}$$

with the argument

$$\mathcal{A}(y,k) = -\frac{\gamma_p}{2}y^2 + \frac{1}{N}\sum_i \ln\cosh(\gamma_p y + \beta k_i) \tag{19}$$

where $k$ denotes the configuration $(k_1, \ldots, k_N)$. The Laplace method allows an asymptotic evaluation of Eq. (18) in the large $N$ limit leading to

$$G_{\text{eff}} = N\mathcal{A}(y_0,k) = -N\frac{\gamma_p}{2}y_0^2 + \sum_i \ln\cosh(\gamma_p y_0 + \beta k_i) \tag{20}$$

with the so-called mean field $y_0$ determined by the saddle point equation

$$y_0 = \frac{1}{N}\sum_i \tanh(\gamma_p y_0 + \beta k_i). \tag{21}$$

Note that the mean field depends explicitly on the sequence $\sigma^{(t)}$ of the recognition site of the target. Having computed an expression for the effective free energy $G_{\text{eff}}$ one can now calculate the desired average

$$\langle\theta_i\rangle_{P(\theta|\sigma^{(t)})} = -\frac{1}{N}\frac{\partial}{\partial k_i}G_{\text{eff}} = \tanh\left(\gamma_p y_0 + \mu_p + \frac{\beta\varepsilon}{2}\sigma_i^{(t)}\right). \tag{22}$$

Additionally one has $\Sigma_i\langle\theta_i\rangle_{P(\theta|\sigma^{(t)})} = Ny_0$ so that the mean field gives the expectation value of the hydrophobicity of the probe ensemble. The free energy difference (12) is then generally given by

$$\Delta F = -\frac{\varepsilon}{2}\left[\sum_i \sigma_i^{(t)}\tanh\left(\gamma_p y_0 + \mu_p + \frac{\beta\varepsilon}{2}\sigma_i^{(t)}\right)\right]_{W^{(t)}} + \frac{\varepsilon}{2}Nh_r[y_0]_{W^{(t)}} \tag{23}$$

where averages over the target and the rival sequences still have to be carried out.

Starting from expression (23) these averages can be carried out numerically. The mean field $y_0$, that is determined by the saddle point equation (21), explicitly depends on the target sequence $\sigma^{(t)}$ and hence one has of the order of $e^N$ saddle point equations for a system with $N$ residues. A particular configuration $\sigma^{(t)}$, however, contains $\Sigma^{(+)}$ hydrophobic residues and $\Sigma^{(-)}$ polar ones. For such a configuration the saddle point equation is given implicitly by the equation

$$y_0(\Sigma^{(+)}, \Sigma^{(-)}) = \frac{\Sigma^{(+)}}{N}\tanh\left(\gamma_p y_0 + \mu_p + \frac{\beta\varepsilon}{2}\right) + \frac{\Sigma^{(-)}}{N}\tanh\left(\gamma_p y_0 + \mu_p - \frac{\beta\varepsilon}{2}\right), \tag{24}$$

and hence the mean field depends only on the numbers $(\Sigma^{(+)}, \Sigma^{(-)})$ for a given configuration. This observation drastically reduces the number of saddle point equations. The remaining equations can be solved using computer algebra programs, the average with respect to the distribution $W^{(t)}$ can be carried out afterwards. A distribution $W^{(t)}$ of the form (6) can be expressed in terms of the density of states $\Omega(\Sigma^{(+)}, \Sigma^{(-)}, E)$ specifying the number of target configurations that are compatible with the macroscopic parameters $\Sigma^{(+)}$, $\Sigma^{(-)}$, and $E$, where $E$ denotes the correlation energy. For fairly small systems this density of states can be calculated exactly by suitable enumeration algorithms [38], for large systems effective Monte Carlos techniques can be applied [39–41].

The mean field treatment reproduces the qualitative results of the numerical investigations discussed in Sec. IV A. For instance, the complementarity of the probe ensemble and the free energy difference as a measure of the recognition ability of the probe-target system in the presence of a rival molecule can now be worked out as a function of the correlation parameter $\gamma_p$. Again a characteristic shift of the opti-

mum correlation parameter and hence correlation length for the two quantities can be observed in accordance with the above discussed numerical Monte Carlo findings.

The mean field result can be used to consider the case of a small correlation parameter $\gamma_p$ (with $\mu_p=0$) in more details. The implicit saddle point equation (24) can be expanded into a power series in $\gamma_p$ and solved up to order $\gamma_p^2$. This gives

$$y_0 = h_t A + \gamma_p h_t B + \gamma_p^2 C_1, \tag{25}$$

with the numerical constants being $A=\tanh(\beta\varepsilon/2)$, $B=\tanh(\beta\varepsilon/2)\mathrm{sech}^2(\beta\varepsilon/2)$, and $C_1=B[h_t-h_t^3\sinh^2(\beta\varepsilon/2)]$. Note that $y_0$ still depends on the particular sequence $\sigma^{(t)}$ of the target through the dependency on the hydrophobicity $h_t=h_t(\sigma^{(t)})=1/N\Sigma_i\sigma_i^{(t)}=(2\Sigma^{(+)}-N)/N$. Using Eq. (25) the complementarity of the probe ensemble averaged over all possible target sequences can be computed up to order $\gamma_p^2$ giving

$$\frac{1}{N}[\langle K\rangle_{P(\theta|\sigma^{(t)})}]_{W^{(t)}} = A + \gamma_p[h_t^2]B + \gamma_p^2[h_t^2]C_2, \tag{26}$$

with $C_2=B[1-\sinh^2(\beta\varepsilon/2)]$. The complementarity is determined in this limit by the second moment of the hydrophobicity distribution of the target molecules and hence directly feels the structure of the hydrophobic and polar patches on the recognition site of the target. For sufficiently large $\beta\varepsilon$ this expression has a maximum at a correlation parameter $\gamma_K=-B/(2C_2)$. Note that the position of the maximum is independent of the properties of the distribution $W^{(t)}$ of the target sequences in the considered situation of a small correlation parameter for the probe molecules, in particular it is independent of the chosen hydrophobicity of the target molecules. The numerical Monte Carlo data shown in Fig. 1 seem to be in accordance with this observation—the data is shown as a function of the correlation length, the maximum shows up at a fairly small correlation length and hence a small correlation parameter. The position where the maximum appears is shifted to smaller values of the correlation parameter and thus correlation length for increased $\beta\varepsilon$. This is again confirmed by the numerical data in Fig. 1. Similarly the free energy difference can be worked out as a second-order Taylor polynomial in $\gamma_p$. It shows a minimum at a correlation parameter $\gamma_F$. The shift $\Delta\gamma_p=\gamma_K-\gamma_F$ can be expressed in terms of the moments of the distribution of the hydrophobic residues on the recognition sites of the target and the rival molecules, respectively,

$$\Delta\gamma_p \sim -\frac{B([h_t^2]-[h_t][h_r])}{2(C_2[h_t^2]-C_1[h_r])} + \frac{B}{2C_2}. \tag{27}$$

Note that $C_1$ depends on $[h_t]$. For the special case where the two types of molecules exhibit the same distribution one has $[h_t]=[h_r]=[h]$. The shift is then dominated by $\Delta\gamma_p\sim[h]^2$ in the asymptotic limit of small values of the hydrophobicity $[h]$. Assuming a linear relation between the correlation length $\lambda_p$ and the correlation parameter $\gamma_p$ in the parameter range where the shift appears—an assumption which should be valid if the shift is small—one also has $\Delta\lambda_p\sim[h]^2$. The numerical Monte Carlo data in Fig. 4 are consistent with this observation, although it should be stressed that the quality of the shown numerical data is not good enough to deduce reliable quantitative statements.

The mean field treatment has been used in this section to obtain an expression for the dependence of the shift of the optimum correlation lengths for the complementarity and the selectivity as a function of the hydrophobicity of the target and rival molecules, respectively. To this end, an expansion in the correlation parameter $\gamma_p$ had been carried out, subsequently an average over the correlated target and rival molecules was performed. The coefficients of the series in $\gamma_p$ therefore basically depend on the moments of the hydrophobicity distribution of these molecules. It has to be noted in this context that the power series in $\gamma_p$ is only an asymptotic one as for the limit $\gamma_p\to 0$ the Hubbard-Stratonovich transformation (17) cannot be applied. Nevertheless, the mean field treatment gives reasonable results for the system with correlated target and rival molecules as the optima of the complementarity and the selectivity show up at nonzero values of the correlation parameter $\gamma_p$. In the case of uncorrelated target and rival molecules, however, this is not the case (compare Fig. 5) and thus the mean field treatment in the discussed framework is not applicable.

## V. MODEL OF DOMINANT COOPERATIVITY

In the previous section the constant $J$ of the cooperative interaction term in Eq. (1) has been set to zero so that only the direct contact interactions due to the hydrophobic effect contribute. In this section the influence of these additional terms is taken into account. This is done by considering the case where the cooperative interactions dominate over the direct contact interactions. In [29] it has been argued that the Hamiltonian can be approximated by

$$\mathcal{H}_{\mathrm{int}}(\sigma,\theta;s) = -\varepsilon\frac{1+s}{2}\sum_{i=1}^{N}\sigma_i\theta_i, \tag{28}$$

in this case with the new (global) interaction variable $s$ taking on the two possible values $\pm 1$. Summing out the variable $s$ and dropping irrelevant constants one ends up with the effective Hamiltonian

$$\mathcal{H}_{\mathrm{eff}} = -\frac{\varepsilon}{2}\sum_i \sigma_i\theta_i - \frac{1}{\beta}\ln\cosh\left(\frac{\beta\varepsilon}{2}\sum_i \sigma_i\theta_i\right) \tag{29}$$

for the sequence $\theta$ of the probe molecule interacting with a molecule whose sequence at its recognition site is specified by $\sigma$. Incorporating the correlation terms (4) the two stage approach to calculate the recognition ability for a system with particular sequences for the target and rival molecules can be carried out. The free energy difference for the interaction of the probe molecules with the target and the rival molecules, respectively, is then given by

$$[\Delta F] = -\frac{\varepsilon}{2}\left[\left\langle\sum_i \sigma_i^{(t)}\theta_i\right\rangle_{P(\theta|\sigma^{(t)})}\right]_{W^{(t)}} + \frac{\varepsilon}{2}N[h_p]_{W^{(t)}}h_r \tag{30}$$

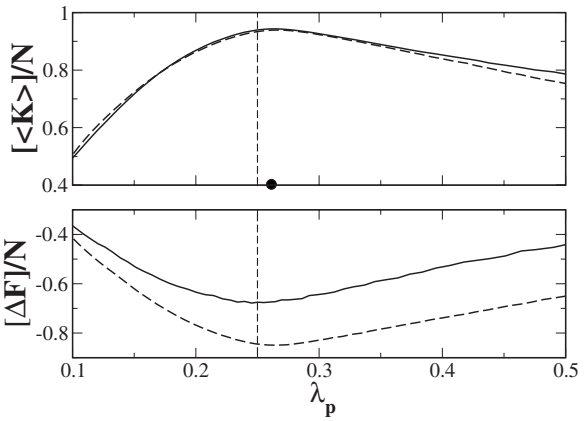


FIG. 6. The complementarity $[\langle K\rangle]/N$ and the free energy difference $[\Delta F]/N$ of the system with dominant cooperative interactions as a function of the correlation length of the probe molecules. The correlation lengths of the target and rival molecules are fixed to the value shown by the circle, the corresponding hydrophobicities are $h_r=h_t=0.5$ (solid line) and $h_r=h_t=0.0$ (dashed line). The optimum correlation length for the recognition ability is clearly shifted to a value below the optimum value for the design of the probe ensemble for the interface with nonzero hydrophobicity.

$$-\frac{1}{\beta}\left[\left\langle \ln\cosh\left(\frac{\beta\varepsilon}{2}\sum_i \sigma_i^{(t)}\theta_i\right)\right\rangle_{P(\theta|\sigma^{(t)})}\right]_{W^{(t)}} + \frac{1}{\beta}\left[\left\langle \ln\cosh\left(\frac{\beta\varepsilon}{2}\sum_i \sigma_i^{(r)}\theta_i\right)\right\rangle_{P(\theta|\sigma^{(t)})}\right]_{W^{(t)},W^{(r)}}. \tag{31}$$

The remaining averages in this expression of the free energy difference can again be worked out by means of Monte Carlo simulations. In Fig. 6 the complementarity of the probe ensemble together with the free energy difference is depicted as a function of the correlation length of the probe molecules. Again the hydrophobicity of the target and rival molecules is fixed, the hydrophobicity of the probe ensemble is unrestricted (i.e., $\mu_p=0$) and adjusts itself during the design step. The data reveal again a shift in the optimum correlation length for the recognition ability compared to the optimum value for the complementarity, although this shift is somehow less pronounced compared to the model with $J=0$. Thus the findings for the uncooperative model are reproduced qualitatively for the model with additional cooperative interactions. Nevertheless a minor difference is visible. Whereas the optimum correlation length with respect to the complementarity of the probe molecules is clearly shifted to a larger value compared to the fixed correlation length of the target molecule in the case of the uncooperative model (compare Fig. 1), the optimum appears (within the accuracy of the numerics) at the same correlation length for the model with dominant cooperativity. This is due to the fact that the cooperative interactions lead to the formation of extended patches of good contacts [29] and thus to an effective reduction of the appearance of defects in the design step, which can also be seen from the fact that the average complementarity at the optimum correlation length is larger for the cooperative model (see Figs. 1 and 6). Thus defects need not be compensated by slightly extending the size of the hydrophobic and polar patches due to correlation effects.

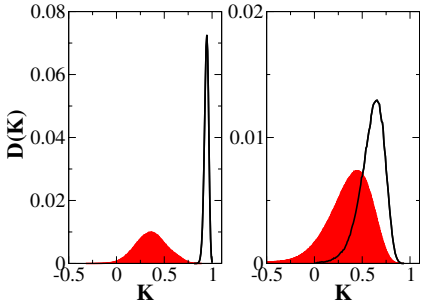


FIG. 7. (Color online) Distribution of the complementarity of the probe ensemble with respect to the target molecules (solid line) and the rival molecules (shaded curve) for different correlation lengths on the recognition site of the probe molecules within the model of dominant cooperativity (28). On the left-hand side the correlation length $\lambda_p=0.25$, on the right-hand side $\lambda_p=0.75$. The hydrophobicities are $h_t=h_r=0.4$, the correlation lengths of the target and rival molecules are $\lambda_t=\lambda_r=0.263$ in each case.

As in the case of the uncooperative model (8) the distribution function of the complementarity parameter of the probe ensemble with respect to the target and rival molecules, respectively, can be investigated. The corresponding curves in Fig. 7 reveal that one ends up with the same qualitative results as in the case of the uncooperative model. Note that the two distributions are well separated from each other and that the distribution of the complementarity with the target molecules is fairly narrow for the correlation length that corresponds to a large complementarity and selectivity. The width of the distribution of the complementarity with the target is fairly reduced compared to the width of the distribution for the uncooperative model (compare Fig. 3).

In principle the same numerical analysis of the recognition ability can be carried out for arbitrary values of the cooperative interaction constant $J$ in Eq. (1) although in this case an expression such as Eq. (30) for the free energy cannot be worked out and thus the numerical effort is much increased. The free energy can be computed, for example, from the density of states that can be evaluated by means of suitable Monte Carlo methods [39–42]. As we expect the qualitative physical behavior not to change, we do not proceed with such systems in this work.

## VI. SUMMARY AND OUTLOOK

In previous studies we developed coarse-grained lattice models to analyze statistical properties of molecular recognition processes between rigid biomolecules such as proteins [10,28,29]. The general approach consists of two stages, where a design of probe molecules with respect to a given target molecule is carried out first. Afterwards the recognition ability of the probe molecules in an heterogeneous environment with rival molecules is evaluated. Note that the design step is carried out in absence of rival molecules

whereas the testing step includes rival molecules that are structurally different from the target, but compete with them for the probe molecules. In the present work we extended our previous models and incorporated sequence correlations into our coarse-grained Hamiltonian of the interactions across the interface of the two proteins. These correlations affect the distribution of hydrophobic and polar residues on the surfaces of the proteins. We investigated the extended models by numerical Monte Carlo simulations and by mean field methods. Both approaches lead to the same qualitative results. In particular we computed the correlation length at which the optimum of the complementarity of the design step appears. The free energy difference that specifies the selectivity of the target-probe interaction in the presence of rival molecules, shows an optimum at a correlation length that is different from the one corresponding to the optimum of the design step. This shift opens up the opportunity to carry out the design slightly away from the optimum possible way without losing selectivity. This might be relevant in the context of harmful effects due to point mutations during evolution which our design step is intended to mimic. In principle it should be possible to check the appearance of two different correlation lengths for the recognition sites of the two proteins that form a complex from experimental structural data. However, we do not know of a corresponding study of this issue.

## ACKNOWLEDGMENT

This work was funded by the Deutsche Forschungsgemeinschaft within the collaborative research center SFB 613.

[1] B. Alberts, D. Bray, L. Lewis, M. Raf, K. Roberts, and J. Watson, *Molecular Biology of the Cell* (Garland Publishing, Inc., New York, 1994).
[2] *Protein-Protein Recognition*, edited by C. Kleanthous (Oxford University Press, Oxford, 2000).
[3] N. A. Peppas and Y. Huang, Pharm. Res. **19**, 578 (2002).
[4] K. Sneppen and G. Zocchi, *Physics in Molecular Biology* (Cambridge University Press, Cambridge, 2005).
[5] M. Delaage, in *Molecular recognition mechanisms*, edited by M. Delaage (VCH Publishers, New York, 1991), p. 1.
[6] L. Pauling and M. Delbrück, Science **92**, 77 (1940).
[7] E. Fischer, Ber. Dtsch. Chem. Ges. B **27**, 2984 (1894).
[8] D. E. Koshland, Proc. Natl. Acad. Sci. U.S.A. **44**, 98 (1958).
[9] S. Wodak and J. Janin, Adv. Protein Chem. **61**, 9 (2003).
[10] H. Behringer, T. Bogner, A. Polotsky, A. Degenhard, and F. Schmid, J. Biotechnol. **129**, 268 (2007).
[11] D. Lancet, E. Sadovsky, and E. Seidemann, Proc. Natl. Acad. Sci. U.S.A. **90**, 3715 (1993).
[12] J. Janin, Proteins: Struct., Funct., Genet. **25**, 438 (1996).
[13] J. Janin, Proteins: Struct., Funct., Genet. **28**, 153 (1997).
[14] S. Rosenwald, R. Kafri, and D. Lancet, J. Theor. Biol. **216**, 327 (2002).
[15] J. Wang and G. M. Verkhivker, Phys. Rev. Lett. **90**, 188101 (2003).
[16] T. Bogner, A. Degenhard, and F. Schmid, Phys. Rev. Lett. **93**, 268108 (2004).
[17] J. Bernauer, A. Poupon, J. Azé, and J. Janin, Phys. Biol. **2**, S17 (2005).
[18] M. Bachmann and W. Janke, Phys. Rev. E **73**, 020901(R) (2006).
[19] D. B. Lukatsky, K. B. Zeldovich, and E. I. Shakhnovich, Phys. Rev. Lett. **97**, 178101 (2006).
[20] M. J. Muthukumar, J. Chem. Phys. **103**, 4723 (1995).
[21] D. Bratko, A. K. Chakraborty, and E. I. Shakhnovich, Chem. Phys. Lett. **280**, 46 (1997).
[22] A. J. Golumbfskie, V. S. Pande, and A. K. Chakraborty, Proc. Natl. Acad. Sci. U.S.A. **96**, 11707 (1999).
[23] A. K. Chakraborty, Phys. Rep. **342**, 1 (2001).
[24] A. Polotsky, A. Degenhard, and F. Schmid, J. Chem. Phys. **120**, 6246 (2004).
[25] A. Polotsky, A. Degenhard, and F. Schmid, J. Chem. Phys. **121**, 4853 (2004).
[26] J. D. Ziebarth, J. Williams, and Y. Wang, Macromolecules **41**, 4929 (2008).
[27] D. B. Lukatsky and E. I. Shakhnovich, Phys. Rev. E **77**, 020901(R) (2008).
[28] H. Behringer, A. Degenhard, and F. Schmid, Phys. Rev. Lett. **97**, 128101 (2006).
[29] H. Behringer, A. Degenhard, and F. Schmid, Phys. Rev. E **76**, 031914 (2007).
[30] J. Janin, F. Rodier, P. Chakrabarti, and R. P. Bahadur, Acta Crystallogr., Sect. D: Biol. Crystallogr. **63**, 1 (2007).
[31] S. Jones and J. M. Thornton, Proc. Natl. Acad. Sci. U.S.A. **93**, 13 (1996).
[32] H. Li, C. Tang, and N. S. Wingreen, Phys. Rev. Lett. **79**, 765 (1997).
[33] M. K. Gilson, J. A. Given, B. L. Bush, and J. A. McCammon, Biophys. J. **72**, 1047 (1997).
[34] M. B. Jackson, *Molecular and Cellular Biophysics* (Cambridge University Press, Cambridge, 2006).
[35] T. A. Larsen, A. J. Olson, and D. S. Goodsell, Structure (London) **6**, 421 (1998).
[36] K. Binder, M. Nauenberg, V. Privman, and A. P. Young, Phys. Rev. B **31**, 1498 (1985).
[37] A. Jayaraman, C. K. Hall, and J. Genzer, Phys. Rev. Lett. **94**, 078103 (2005).
[38] K. Binder, Physica (Amsterdam) **62**, 508 (1972).
[39] A. Hüller and M. Pleimling, Int. J. Mod. Phys. C **13**, 947 (2002).
[40] F. Wang and D. P. Landau, Phys. Rev. Lett. **86**, 2050 (2001).
[41] D. P. Landau, S. Tsai, and M. Exler, Am. J. Phys. **72**, 1294 (2004).
[42] P. Virnau and M. Müller, J. Chem. Phys. **120**, 10925 (2004).