

## Statistical properties of contact vectors

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We study the statistical properties of *contact vectors*, a construct to characterize a protein's structure. The contact vector of an  $N$ -residue protein is a list of  $N$  integers  $n_i$ , representing the number of residues in contact with residue  $i$ . We study analytically (at mean-field level) and numerically the amount of structural information contained in a contact vector. Analytical calculations reveal that a large variance in the contact numbers reduces the degeneracy of the mapping between contact vectors and structures. Exact enumeration for lengths up to  $N=16$  on the three-dimensional cubic lattice indicates that the growth rate of number of contact vectors as a function of  $N$  is only 3% less than that for contact maps. In particular, for compact structures we present numerical evidence that, practically, each contact vector corresponds to only a handful of structures. We discuss how this information can be used for better structure prediction.

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### I. INTRODUCTION

The protein-folding problem has been the subject of extensive research in the last decade and although much has been learned a satisfactory understanding of the phenomenon has not been reached yet [1–3]. The physical approach to the problem is to consider the native state of a protein as the ground state of a Hamiltonian that acts on sequence space and summarizes the interresidue and residue-solvent interactions [1,2,4]. Recently it was shown that there are several cases for which there is no possible choice of pairwise contact interactions between residues that suffices to pin down the native state even for a single protein [5,6]. This conclusion is supported by molecular dynamics studies [7] and lattice models [8] on residue-solvent interactions, where many-body forces are shown, or can be deduced to be as relevant as two-body forces. To get around this failure of the two-body Hamiltonian approach while retaining a coarse-grained description (as opposed to, say, an all-atom one, including water [9]), we need to introduce new terms at the residue level to bias the optimization procedure towards the true minima.

It is widely accepted that hydrophobicity is the force driving the folding process [10]. At the individual residue level, hydrophobicity is correlated with the solvent-exposed surface area in the native state [11]. In addition, as reported below, a statistical analysis of the native structures deposited in the protein data bank (PDB) [12] reveals a good correlation (coefficient of correlation 0.8) between the solvent-hidden surface area per residue and the number of interresidue contacts per residue in the native state. We, therefore, propose the following two-step procedure for predicting the native state of a protein. First, a reasonably accurate prediction of the exposed surface area in the native fold is made on the basis of sequence information [11]. Second, this information is translated into a prediction of the number of native contacts of each residue, e.g., to a predicted native *contact vector*. Even if this scheme will turn out to be insufficient to

perform a successful prediction, it opens the possibility to confine the search for the native fold to a small portion of the conformational space. The question then becomes “How many folded configurations are there, consistent with a given set of contact numbers?” And, for that matter, “Is such a contact-number representation of the protein structure degenerate at all?” The rest of this paper addresses these questions.

### II. CONTACT MAPS VS CONTACT VECTORS

The contact map (CM) [13] of a protein of  $N$  amino acids is a symmetric binary matrix  $C$  of size  $N \times N$ , such that  $C_{ij} = 1$  when the  $i$ th and the  $j$ th amino acids of the sequence are neighbors, with some suitable definition of “neighborhoodness” (e.g., a common construct is to threshold the pairwise distance matrix for the  $C_\alpha$  atoms [5]). The CM has proven to be a convenient encoding of the three-dimensional native fold: (1) The native backbone conformation can be reproduced to within  $\sim 1.5$  Å average uncertainty (the same as most x-ray data) [14], and (2). It allows for an efficient search of the configuration space, since large conformational changes can be obtained by minor modifications of the CM [15]. Within such minimalistic framework one hopes to gain new insight to the protein-folding problem since it is amenable to different physical and mathematical tools. For instance, the following Hamiltonian acting on the contact map space has been extensively used in the past [16–19]:

$$H = \sum_{ij} w(\alpha_i, \alpha_j) C_{ij}, \quad (1)$$

where  $w(\alpha, \beta)$  is one of the 210 energy parameters representing the contact energy between the amino-acid types  $\alpha$  and  $\beta$ . Unfortunately, this formulation has limited predictive power. For example, given a large enough set of sequences and decoys (obtained by threading) from the PDB, no set of  $w(\alpha, \beta)$  exists, for which  $H$  has its ground states at the native folds [6]. This is in accordance with the recent studies on

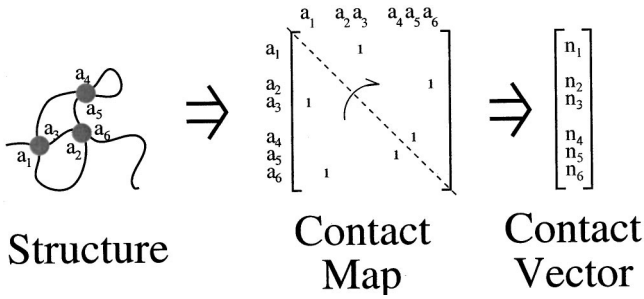


FIG. 1. The contact map is a binary representation of the three-dimensional structure of the folded protein. The contact vector is constructed by summing up the rows of the contact map.

the nature of the hydrophobic interaction [7,8], whose conclusion is that many-body interactions are of the same order of magnitude as two-body interactions.

One possible way to improve the Hamiltonian in Eq. (1) is to include an energy penalty for deviations from the native contacts,

$$H = (1 - \lambda) \sum_{ij} w(a_i, a_j) C_{ij} + \lambda \sum_i (n_i - n_i^{\text{nat}})^2 \quad (2)$$

where we define a “contact vector” (CV)  $\vec{n}$  of rank  $N$ , which is the sum of the entries of the CM on each row (or column) (see Fig. 1),

$$n_i = \sum_j C_{ij}. \quad (3)$$

Contact vectors have already been studied in the context of protein folding [20–28]. We note, in particular, that the second term in Eq. (2) resembles a hydrophobic term introduced previously [29] and studied in Ref. [30], with the difference that the desired number of contacts of residue  $i$  is determined by its species. Here instead we assume the knowledge of  $n_i^{\text{nat}}$ , the correct number of contacts of residue  $i$  in the native structure. Hence the second term in Eq. (2) carries the same spirit as the Go model [31]. In this paper we are interested in studying the statistical properties of contact vectors. For our more general purpose, it would seem inconsistent to use Eq. (2) to predict the native structure of a protein, as we bias the Hamiltonian towards the minimum by using information that is not accessible to us before we actually solve the problem. However, unlike in the Go model, the information required here about the native state (the number of contacts for each residue) is modest, and, most crucially, can be predicted. Learning algorithms have been recently developed, which are trained on known structures to predict the surface exposure of the amino acids in the native fold [11,32]. Since the hydrophobic effect is driving the folding process [10], it is natural to expect that an accurate prediction of the solvent exposed surface of each residue in the folded state may lead to prediction of the correct native structure. To bridge the gap between the exposed-surface information and the CV defined above, we performed an analysis on a representative set of proteins from the PDB database. We found a linear correlation with a coefficient of correlation

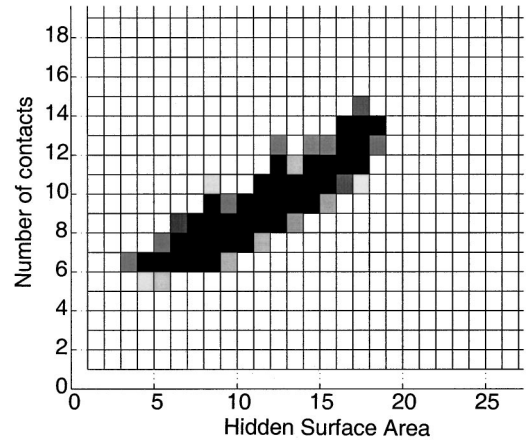


FIG. 2. Hidden surface area per residue (after appropriate scaling) vs number of contacts per residue. The histogram is obtained by averaging over 177 representative proteins with a threshold on the  $C_\alpha$  distance between amino-acid pairs [5]. The number of occurrences is gray-scale coded, increasing from 0 (white) to 500 (black). The coefficient of correlation is 0.8.

of 0.8 between the solvent *hidden* surface area of a residue and the number of amino acids it is in contact with (see Fig. 2). Therefore, in future work we expect to replace the  $n_i^{\text{nat}}$  term in Eq. (2) by  $n_i^{\text{predicted}}$ , thereby breaking the causality loop that is a characteristic of Go-like models. Another reason to study the model of Eq. (2) is that a related kind of Hamiltonian has been recently proved to be useful to determine the structure of nearly native protein conformations [33]. In that study,  $n_i$  represents the number of *native* contacts formed by residue  $i$  in the contact map  $C$ . Also in that case, it was found that a large variance in  $n_i$  (see below) implies a low degeneracy in mapping between contact vectors and three-dimensional conformations.

In studying Eq. (2), first we tried to use a set of contact energy parameters  $w(a_i, a_j)$ , found earlier by an optimization process, using Eq. (2) with  $\lambda = 0$ . This attempt failed to assign the minimal energy to the native state for any choice of  $\lambda$ . However, an optimization of  $w(\alpha, \beta)$  over the known structures by using the Hamiltonian in Eq. (2) with  $\lambda \neq 0$  may, perhaps, successfully identify the native state. We will investigate this possibility in the future.

The Hamiltonian Eq. (2), with  $\lambda = 1$ , fails to identify the native fold. This statement means that it is possible to find conformations that, on the one hand, are very different from the native one and, on the other, each amino acid has exactly the correct number of neighbors, that is the same number of neighbors as in the native state. This result was first found by Ejtehadi *et al.* [22] by exact enumeration of all the compact conformations on a  $3 \times 3 \times 3$  cubic lattice. For actual proteins, an example is given in Fig. 3 in the case of protein CI2 (PDB code 2ci2), where the CM’s of the native fold and of another conformation are superimposed. These two conformations have identical CV’s. At first glance, it would seem unlikely to find two compact configurations where each residue has exactly the same number of neighboring residues in contact. On the other hand, the cautious reader will attribute this degeneracy to the loss of information [from

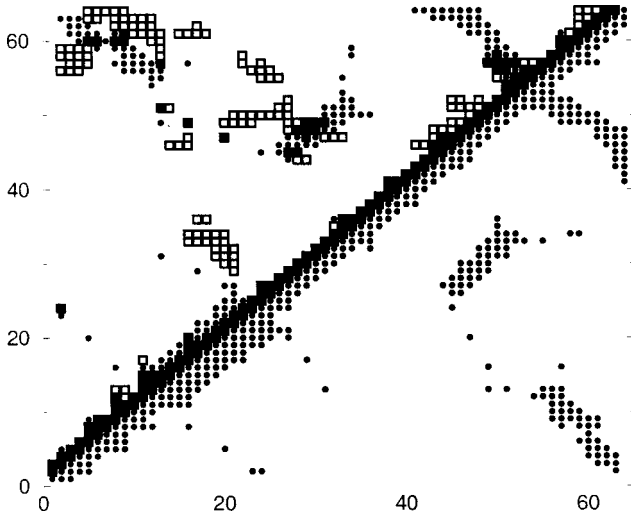


FIG. 3. The native contact map (circles) of protein CI2 (PDB code 2ci2) and a nonnative map (squares) with the same contact vector are overlapped. For clarity, the symmetric half of the nonnative contact map is omitted.

$N(N-1)/2$  binary variables to  $N$  integers of size  $\leq N$ ] associated with going from a given CM to its corresponding CV via Eq. (3). Quantifying the resulting degeneracy is a nontrivial problem. The following section is an analytical attempt in this direction.

### III. AN ANALYTICAL APPROACH

We ask the following question: “How many contact maps exist for a given contact vector  $\vec{n}$ ?” In fact, we should be

counting, for a given  $\vec{n}$ , only the *physical* CM’s that are consistent with it. A physical CM [14,29] is one for which a perfectly matching chain configuration can be found. There is, however, no known analytical selection rule for the physical CM’s among all symmetric and traceless  $N \times N$  matrices; therefore, in our analytic study we will consider all binary symmetric matrices. This is essentially the mean-field treatment of the problem, since in the limit of infinite dimensions, all the constraints on the CM, except being symmetric with zero trace, will be relaxed. For any finite dimension we overestimate the degeneracy—the number of physical CM’s scales exponentially, as  $e^N$ , whereas the number of possible CM’s scales as  $e^{N^2}$  [13].

Since we deal with contact maps, we will consider symmetric, traceless binary matrices, characterized by  $x_{ij}=x_{ji}$  and  $x_{ii}=0$ . The formal expression for the number  $d(\vec{n})$  of such matrices consistent with a given contact vector  $\vec{n}$  is

$$d(\vec{n}) = \sum_{\{x_{ij}\}} \prod_{i=1}^N \delta_{(\sum_j x_{ij}), n_i}, \quad (4)$$

where the sum over  $j$  in the Kronecker  $\delta$  runs over entire rows of the matrix. The sum over  $x_{ij}=0, 1$  represents a trace over all binary matrices, and the constraint  $i > j$  ensures that the sum is over  $N(N-1)/2$  binary variables. In order to perform the summation, we rewrite the Kronecker  $\delta$  as a discrete Fourier sum,

$$d(\vec{n}) = \sum_{\{c_{ij}\}} \prod_{i=1}^N \left( \frac{1}{N} \sum_{k=0}^{N-1} \exp \left[ i 2 \pi \frac{k}{N} \left( \sum_j x_{ij} - n_i \right) \right] \right) = \frac{1}{N^N} \sum_{k_1=0}^{N-1} \sum_{k_2=0}^{N-1} \cdots \sum_{k_N=0}^{N-1} \left( \sum_{\{x_{ij}\}} \exp \left[ i \frac{2\pi}{N} \sum_i k_i \left( \sum_j x_{ij} - n_i \right) \right] \right). \quad (5)$$

Scaling  $k_i$  by  $N$ , approximate the sums by integrals. Then, evaluate the trace over the matrix elements, paying special attention to  $x_{ij}=x_{ji}$  and  $x_{ii}=0$ ,

$$d(\vec{n}) = \int_0^1 dk_1 dk_2 \cdots dk_N \left( \sum_{\{x_{ij}\}} \exp \left[ i 2 \pi \sum_i k_i \left( \sum_j x_{ij} - n_i \right) \right] \right) = 2^{N(N-1)/2} \int_0^1 dk_1 dk_2 \cdots dk_N \times \exp \left\{ -i 2 \pi \sum_i k_i [(N-1)/2 - n_i] \right\} \prod_{i>j} \cos[\pi(k_i + k_j)]. \quad (6)$$

The integral can now be evaluated around its saddle points,  $k_i=1/2$  and  $k_i=0,1$ , which contribute equally. After we set  $k_i = 1/2 + q_i$  and assume  $N$  is divisible by 4, we obtain

$$\simeq 2^{N(N-1)/2} \int_{-1/2}^{1/2} dq_1 dq_2 \cdots dq_N \exp \left\{ -i 2 \pi \sum_i q_i [(N-1)/2 - n_i] - (\pi^2/2) \left[ N \sum_i q_i^2 + \left( \sum_i q_i \right)^2 \right] \right\}. \quad (7)$$

The last square term in the exponent can be eliminated by a Hubbard transformation after rescaling  $q_i$  by  $\sqrt{N}$  and defining  $\eta_i = n_i - (N-1)/2$

$$d(\vec{n}) \approx 2^{N(N-1)/2} \sqrt{\frac{2}{\pi}} \int_{-1/2}^{1/2} dq_1 dq_2 \dots dq_N \int_{-\infty}^{\infty} dy \exp\left(-y^2/2 + i\pi y \sum_i q_i + i2\pi \sum_i \eta_i q_i - N\pi^2/2 \sum_i q_i^2\right),$$

which finally simplifies to yield

$$d(\vec{n}) \approx \frac{2^{N^2/2}}{(N/\pi)^{N/2} \sqrt{N}} e^{-2\sigma_\eta^2 - \bar{\eta}^2}, \quad (8)$$

where  $\bar{\eta}$  and  $\sigma_\eta$  are the average and the standard deviation of  $\eta_i = (n_i - N/2)$ . This is a mean-field estimate of how the degeneracy of a CV scales with respect to the statistical properties of the CV. The leading behavior is clearly far from being realistic, since the degeneracy should scale at most as  $z^N$  for some  $z < z_{CM}$  [ $\ln(z_{CM})$  is 0.83 in two dimensions (2D) [13] and 1.32 in 3D as calculated here]. Equation (8) further suggests that the maximally degenerate CV with a fixed average number of contacts has  $\sigma_\eta = 0$ , i.e., all the amino acids have an equal number of contacts, whereas an unbiased sample of CV's will be dominated by those vectors with a typical standard deviation of  $\sigma_\eta \approx \sqrt{N}$ . The mean-field message is that the degeneracy is a decreasing function of  $\sigma_\eta$ , i.e., variation in contact number is desirable for low degeneracy. In the following section, we argue that this is true away from the saddle point as well.

#### IV. FINITE CONNECTIVITY: GRAPH COUNTING

In the preceding section, we allowed for the number of contacts to take any value between 0 and  $N$ . In reality, and also in lattice models, the number of contacts is of order unity. Therefore, it is desirable to have an estimate of the degeneracy of such CV's. Once again, we consider all traceless, symmetric, binary  $N \times N$  matrices. We first observe that every such matrix encodes a unique graph with  $N$  vertices, a

vertex pair being connected if the corresponding matrix element is 1. Symmetry ensures that the graph is undirected. We can ensure chain connectivity (but not the graph being physical!) by freezing connections on the first off diagonal; if we choose to relax these ‘‘backbone connections,’’ the remaining graph need not be connected.

The degeneracy of a CV, can then be approximated by the number of graphs with  $N$  vertices and given connectivities. We imagine the vertices from 1 to  $N$  with a corresponding number of legs sticking out of each and we ask in how many ways these legs can be connected such that none will be left out (the total number of legs is an even number). Equation (9) follows immediately if one imagines connecting pairs of legs sequentially (the numerator) and remembering that legs coming out of the same vertex are interchangeable (denominator).

Let's assume we allow the entries of the CV to be one of  $0, 1, \dots, n$ ,  $n \ll N$ , and the composition given by  $\{p_0, p_1, \dots, p_n\}$ ,  $p_i N \equiv N_i$  being the number of amino acids with  $i$  contacts. The average number of contacts is  $\sum_i i p_i \equiv c$ . The corresponding number of graphs reads

$$d(N, \{p_i\}) = \frac{(cN-1)!!}{(0!)^{N_0} (1!)^{N_1} \dots (n!)^{N_n}}. \quad (9)$$

(The only difference with the usual Feynman diagram counting is the missing  $N!$  in the denominator: our vertices are distinguishable since they correspond to the amino acids labeled by their sequence number.)

Note that this expression is an approximation to the number of symmetric traceless CM's, since diagrams with small loops involving one vertex, as well as with more than one line connecting the same two vertices are counted in Eq. (9), even though they do not correspond to any CM's. However, corrections due to excluding such diagrams do not change the scaling with  $N$ . Applying Stirling's formula to Eq. (9),

$$d(\{p_i\}) \approx \exp\left\{\frac{cN}{2} \ln N + N \left[\frac{c}{2} \ln c - 1 - \sum p_n \ln(n!)\right]\right\}. \quad (10)$$

The leading order is now  $z_F^{N \ln N}$  with  $z_F = e^{c/2}$ . Better estimations require taking into consideration the spatial correlations in the contact numbers due to the underlying one-dimensional chain. Our next task is to find the compositions with the minimum and maximum degeneracy. The leading order in Eq. (10) depends only on the total number of contacts, so it is sensible to confine the search into the subspace of CV's with a fixed average connectivity. We then extremize the next order term with respect to  $\{p_i\}$ , subject to the constraints  $\sum p_m = 1$  and  $\sum m p_m = c$  to find which distribution of contacts allows for the better ‘‘designability’’ (i.e., less degeneracy). Figure 4 shows the choice of  $\{p_i\}$  with maximum/

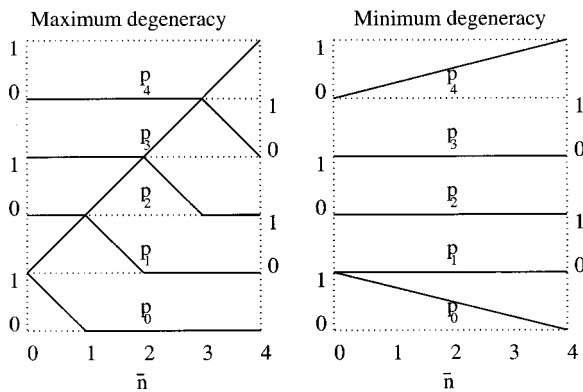


FIG. 4. Solution of the mean-field equations for the maximal and minimal degeneracy of contact vectors with finite average contact number. Maximum contact number is chosen to be 4 as for the cubic lattice. The solution for each  $p_i$  is drawn within the corresponding horizontal band. The y axis of each band is labeled on the left and right alternately. For fixed average contact number,  $c$ , lowest degeneracy is when the standard deviation in the contact numbers is maximal, and vice versa.



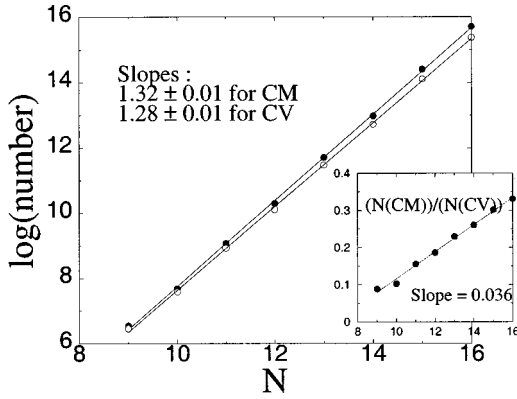


FIG. 5. Scaling of number of contact maps ( $N_{cm}$ ) and the number of contact vectors ( $N_{cv}$ ) with the chain length, obtained by exact enumeration on the three-dimensional cubic lattice. The inset (also a linear-natural log plot) shows the scaling of the ratio between  $N_{cm}$  and  $N_{cv}$ .

minimum degeneracy obtained numerically, as a function of the average contact number  $c$  (maximum number of non-backbone contacts  $n$  is chosen to be 4 as for the cubic lattice). As read from the graphs, the highly degenerate scenario is when the number of contacts for each residue is minimally away from the average, and vice versa for the low degeneracy. Even though here we deal with low connectivity  $n_i \ll N$ , whereas in the preceding section we had  $n_i \sim N$ , the result obtained here is the same as there—low degeneracy goes in parallel with maximal variation in contact number.

One application of this principle is an order of magnitude estimation for the “optimal” length for a protein. Consider a necklace model of the protein, each residue represented by a sphere of fixed radius, and the necklace itself folded into a large compact sphere, where compactness is imposed as a necessary condition for stability. Then, maximal contact number fluctuation is attained when the number of buried residues equals the number of residues on the surface. From this purely geometric construction, one can estimate an “ideal” chain size: Let the radii of the individual residues be unity, and the radius of the protein be  $R$ . Assuming  $hcp$ -like packing, each residue occupies a volume of  $v = 4\sqrt{2}(\text{unit})^3$ , and those on the surface cover, roughly,  $a = 4(\text{unit})^2$  of surface area. Then, if  $N$  is the number of residues, we have  $vN = 4\pi R^3/3$  and  $aN/2 = 4\pi R^2$ , which yields  $N \sim 450$ .

## V. NUMERICAL RESULTS

To compare the analytical findings presented above with numerical simulations, we performed several exact enumeration studies on the square and the cubic lattices. Therefore, in this section, we deal with physical CM’s and contact vectors, i.e., those generated by self-avoiding walks in two and three dimensions. In each analysis, we kept a record of the distinct CM’s we encountered and the corresponding CV’s. Our first observation is that, the number of distinct CV’s for a given size  $N$  scales exponentially with  $N$

$$N_{cv} \sim e^{a_{cv}N}.$$

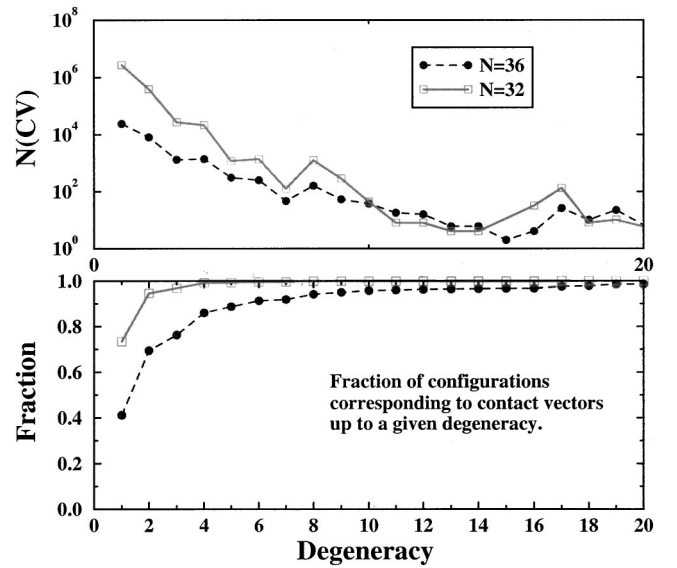


FIG. 6. Contact vector degeneracy for SAW’s within a  $6 \times 6$  square. The upper graph is a linear-log plot of the number  $N_{cv}$  of distinct contact vectors with a given degeneracy. The lower graph shows the fraction of SAW’s of lengths 32 and 36 corresponding to contact vectors up to a given degeneracy.

For given  $N$ , the number of CV’s, CM’s, and self-avoiding walks increase in the given order. Yet, it is interesting that the growth rate  $a_{cv} = 1.28 \pm 0.01$  is only about 3% less than the corresponding rate  $a_{cm} = 1.32 \pm 0.01$  for the CM’s in three dimensions (see Fig. 5, and also [13]). The discrepancy between the mean-field analytical calculations and the exact enumeration results points to the fact that the finite dimensionality and the correlations between contacts due to the underlying one-dimensional chain (i.e., working with physical CM’s and CV’s) are crucial.

The almost identical growth rates are in accordance with our next analysis on the compact configurations on a  $6 \times 6$  square lattice (see [34]). Considering all the Hamiltonian walks within a  $6 \times 6$  square, we identified the number of walks that correspond to each CV and found that the number of CV’s with degeneracy  $d$  drops more or less exponentially with  $d$  (see Fig. 6). In fact, more than 96% of all the contact vectors have degeneracy  $d \leq 6$ , although it is possible to find a vector with 69 Hamiltonian walks mapped on it (not shown in Fig. 6). The degeneracy gets even smaller in the case of a compact but less than perfect packing. In our case this happens when the  $6 \times 6$  square is mostly filled with a 32-residue chain. Introduced vacancies, especially when in the core, “label” some of the residues with an otherwise identical contact number. Rearrangement of the core, where all the residues have identical number of contacts, is the dominant mechanism of degeneracy. Hence, it gets more difficult to find conformations with the same CV, once this degeneracy is lifted by the vacancies. In this case, for practically all the CV’s we have  $d \leq 5$ . It will be interesting, in a future research, to extend this analysis to the cubic lattice and also to test numerically our mean field prediction that the degeneracy decreases with  $\sigma$ . About the latter issue, on the square lattice our preliminary results indicate that our predictions

are consistent with the numerical results for a small number of contacts, but the agreement deteriorates for higher contact numbers. An unambiguous answer to this problem is difficult owing to the small system sizes amenable to complete enumeration. On the cubic lattice the problem is made even more difficult by the fact that, for accessible lengths, practically all the residues are on the surface.

## VI. CONCLUSION

Existing and future prediction methods for the accessible surface area of individual residues can be adopted to predict the number of native contacts of each amino acid of a given protein. This prediction can then be used for an efficient search of the native contact map (and the corresponding conformation) in a dramatically reduced configuration space. The prerequisite of such a program is to be able to identify different folds consistent with a given set of contact numbers for each residue. We investigated at the mean-field level the partition of the configuration space (or rather the contact map space) into degeneracy classes labeled by the CV's. The average degeneracy predicted by the analytical calculations disagrees with the numerical findings, indicating that the finite dimensionality and the correlations induced by the underlying one-dimensional chain are crucial even for a qualitatively satisfactory result. We did find, already at the mean-field level, that increasing the fluctuations in the native contact numbers reduces the degeneracy of contact vectors. This finding is also supported by another analytical calculation, valid in a different regime, where the average contact number is  $O(1)$ .

We further investigated by exact enumeration the degen-

eracy spectrum of CV's for self-avoiding walks on the square and the cubic lattice. We found that for compact self-avoiding walks the CM and the CV representations carry nearly the same amount of information. This is an encouraging result, for an accurate enough prediction of solvent exposed surface areas in the native state may then be used to reduce the search space sufficiently, so that within the limited set of remaining candidate CM's a simple pairwise interaction potential may suffice to single out the native fold of the protein. In addition, we performed exact enumeration over all self-avoiding walk (SAW's) of  $N \leq 16$  steps in three dimension, and found that the number of CV's grows exponentially with the protein length, with a prefactor only a few percent smaller than that for the CM's. The slow exponential growth of the average degeneracy of the CV's is largely overestimated by our mean-field calculations. Further analytical and numerical research is certainly called for. We also observed that for *compact* configurations, CV $\rightarrow$ CM mapping is practically one to few. The Hamiltonian in Eq. (1), therefore, may still be promising if the pairwise interactions are optimized within the context of a (even roughly) predicted CV.

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