Exactness of the cluster variation method and factorization of the equilibrium probability for the Wako–Saitô–Muñoz–Eaton model of protein folding

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Abstract. I study the properties of the equilibrium probability distribution of a protein folding model originally introduced by Wako and Saitô, and later reconsidered by Muñoz and Eaton. The model is a one-dimensional model with binary variables and many-body, long-range interactions, which has been solved exactly through a mapping to a two-dimensional model of binary variables with local constraints. Here I show that the equilibrium probability of this two-dimensional model factors into the product of local cluster probabilities, each raised to a suitable exponent. The clusters involved are single sites, nearest-neighbour pairs and square plaquettes, and the exponents are the coefficients of the entropy expansion of the cluster variation method. As a consequence, the cluster variation method is exact for this model.

Keywords: solvable lattice models, structures and conformations (theory), exact results
1. Introduction

The cluster variation method (CVM) is an approximate method of equilibrium statistical physics introduced by Kikuchi [1] as a generalization of the Bethe–Peierls [2, 3] and Kramers–Wannier [4, 5] approximations. In its modern formulation [6] it is based on the minimization of an approximate variational free energy which is derived from the exact one by a truncation of the cumulant expansion of the entropy. This free energy depends on the probability distributions of local clusters. An account of the CVM and its applications up to the beginning of the 1990s can be found in [7]. A review of more recent results has just appeared [8].

Recently the relationship between the Bethe–Peierls approximation, that is the lowest order CVM approximation, and the belief propagation method [9], widely used for inference and optimization problems defined in terms of probabilistic graphical models, has been discovered [10, 11], and this has led to the development of the so-called generalized belief propagation (GBP) [10], an iterative message-passing algorithm whose fixed points are stationary points of the CVM free energy.

There are only a few cases in which the CVM, and hence the GBP algorithm, gives exact results. In most cases the exactness is due to the tree-like topological structure of the underlying lattice or graph. Leaving apart tree-like structures, the only case for which I am aware of the exactness of the CVM is that of disorder varieties [12, 13], which occur in two-dimensional Ising models with short-range competitive interactions on ordinary translation-invariant lattices, where the correlations have a particularly simple form which resembles that of one-dimensional models.

In all the cases in which the CVM is exact, independent of the reason, the equilibrium probability distribution factors into a product of local cluster probabilities, each raised to a suitable integer exponent.

Given the limited number of cases in which the CVM gives an exact solution, it is particularly relevant to show that for a particular protein folding model the CVM is exact and the equilibrium probability factors. This is the purpose of the present paper.

The model I am going to study was introduced and exactly solved for the first time in 1978 by Wako and Saitô [14, 15], who showed its potential application to the protein
folding problem. Much later, Muñoz and Eaton [16]–[18] reconsidered this model, in a slightly different formulation, solved it within the so-called single (double, triple) sequence approximation, and made comparisons with their own experimental data, after which the model became rather popular (see for instance [19]). Flammini et al [20] derived a mean-field theory, made Monte Carlo simulations and solved exactly the α-helix case, and later Bruscolini and I [21,22] solved exactly the general case, using ideas that are essentially the same as those by Wako and Saitō [14,15]. The same model and techniques have recently been used for strained epitaxy on a modulated substrate [23].

In all these papers no reference was ever made to the original works by Wako and Saitō. As far as I know, the first paper citing both Wako–Saitō and Muñoz–Eaton is due to Itoh and Sasai [24], which refers to the model as the Wako–Saitō–Muñoz–Eaton (WSME) model, as I will do in the following.

The WSME model is a one-dimensional effective model, where a given protein is regarded as a sequence of monomers (residues) connected by peptidic bonds, and a binary variable is associated to each peptidic bond, with the value 1 representing the folded (or native) configuration and the value 0 representing the unfolded configuration. An entropic cost is associated to the folded configuration. Only native interactions are considered, like in Gō [25] models; that is, two residues are allowed to interact only if they are in contact in the native state. Moreover, and this is the main characteristic of the present model, two residues can interact only if all the peptidic bonds between them in the sequence are in the native state, which gives rise to the many-body, long-range interactions.

The exact solution of the equilibrium thermodynamics of the model can be obtained through a mapping to a two-dimensional model [21], defined on a triangular-shaped portion of the square lattice, with local constraints as the only interactions. The dimension of the state space of a row of this model is at most equal to the length of the protein and this makes the transfer matrix approach feasible.

In the present paper I show that the equilibrium probability distribution of this model in its two-dimensional version can be written in a factorized form which is typical of generalized mean-field theories. It is a product of local cluster probabilities, marginals of the global probability. In this product only single-site, nearest-neighbour (NN) and square plaquette clusters appear, and the corresponding probabilities are raised to exponents which are the coefficients of the entropy expansion which appears in the formulation of the CVM [6]. As a consequence, the CVM turns out to be exact (which was already noticed empirically in [21]), providing an exact variational free energy depending on a number of variables which scales only quadratically with the length of the protein.

The plan of the paper is as follows. In section 2 the model is described in detail, its mapping to a two-dimensional model is discussed in section 3, then the factorization of the probability distribution is shown in section 4. The CVM is described in section 5, where its exactness for the present model is shown and the consequences of this property are discussed. Finally, conclusions are drawn in section 6.

2. The model

The WSME model, if considered as a model for protein folding, is a simplified effective model in the sense that one considers a very restricted state space, and imagines to
Integrate with respect to all the degrees of freedom except the binary peptidic bond variables, obtaining a Hamiltonian which is actually an effective free energy.

In order to describe the model, consider a protein of length \( N + 1 \) residues, and associate a binary variable \( m_i, i = 1, \ldots, N \) to each peptidic bond between residues \( i \) and \( i+1 \). \( m_i = 1 \) denotes a peptidic bond in a native configuration, \( m_i = 0 \) a peptidic bond in an unfolded one. Since there are actually many more unfolded configurations than native ones, an entropic cost \( \Delta s_i < 0 \) is associated to each residue.

Two residues are allowed to interact only if they are in contact in the native state. A detailed definition of contact between residues is not needed here and can be found in [16]–[18]. Here I simply assume that a contact matrix \( \Delta \) is given, with elements \( \Delta_{ij} = 1 \) if residues \( i \) and \( j + 1 \) (or, equivalently, peptidic bonds \( i \) and \( j \)) are in contact in the native state, and 0 otherwise.

As a further condition, residues \( i \) and \( j + 1 \) interact (with an energy \( \epsilon_{i,j} \)) only if all the peptidic bonds between them are in the native state; that is, only if \( \prod_{k=i}^{j} m_k = 1 \). We can therefore write the Hamiltonian (effective free energy)

\[
H(m) = N - \sum_{i=1}^{N} \sum_{j=i+1}^{N} \epsilon_{i,j} \Delta_{i,j} \prod_{k=i}^{j} m_k - T \sum_{i=1}^{N} \Delta s_i m_i,
\]

where \( T \) is the temperature.

The remainder of this paper does not focus on the applications to the protein folding problem, but rather on the mathematical properties of the statistical mechanics of the model itself; therefore, from now on we shall deal with a generic Hamiltonian of the form

\[
H(m) = \sum_{i=1}^{N} \sum_{j=i}^{N} h_{i,j} \prod_{k=i}^{j} m_k,
\]

where the \( h_{i,j} \)s can be temperature dependent.

3. Mapping to a two-dimensional model

The above Hamiltonian suggests introducing the new binary variables [21] \( m_{j,i} = \prod_{k=i}^{j} m_k \) (notice the order of the indices), which take value 1 if \( m_k = 1, i \leq k \leq j \), and 0 otherwise. These new variables can be associated to the triangular-shaped portion of the square lattice defined by \( 1 \leq i \leq j \leq N \) and shown in figure 1, and the original variables are included in this set, since \( m_{i,i} = m_i \).

The Hamiltonian can now be written as

\[
H(m) = \sum_{j=1}^{N} \sum_{i=1}^{j} h_{i,j} m_{j,i},
\]

but the new variables are not all independent. Since we have a model with \( 2^N \) configurations written in terms of \( N(N + 1)/2 \) binary variables, constraints must exist between these variables. These constraints can be written in different ways, and we chose [21] to write them as

\[
m_{j,i} = m_{j-1,i} m_{j,i+1}, \quad 1 \leq i < j \leq N.
\]
One is therefore left with a model with a local (actually non-interacting) Hamiltonian, and local constraints in place of the interactions. Formally one could also include the constraints into the Hamiltonian, by studying the limit $\lambda \to +\infty$ of

$$H(m) = \sum_{j=1}^{N} \sum_{i=1}^{j} h_{i,j} m_{j,i} + \lambda \sum_{j=2}^{N} \sum_{i=1}^{j-1} (m_{j,i} - m_{j-1,i} m_{j,i+1})^2.$$  \hfill (5)

In the new representation the feasibility of the transfer matrix approach becomes evident. Consider the variables in row $j$ in figure 1, that is $m_j = (m_{j,1}, m_{j,2}, \ldots m_{j,j})$. Because of the constraints all configurations with $m_{j,i} = 1$ and $m_{j,i+1} = 0$ are forbidden, leaving as the only allowed states for $m_j$ the $j+1$ states denoted by $e^k_j$ and defined by

$$m_{j,i} = \begin{cases} 0, & i \leq k \\ 1, & i > k \end{cases}, \quad 0 \leq k \leq j.$$  \hfill (6)

In figure 1 these states are readily depicted by placing $k$ 0s on the left of row $j$ and $j-k$ 1s on the right.

A transfer matrix solution for a protein of length $N+1$ has then to deal with the product of $N-1$ matrices, the largest of which has size $(N+1) \times N$; the number of operations involved grows polynomially in $N$, and the model can be easily solved even for long proteins.

4. Factorization of the probability distribution

The existence of a row-to-row transfer matrix is intimately connected to the factorization of the model’s probability distribution over rows. This is well known in statistical
mechanics (see for instance [26]). Readers interested in a purely statistical formulation will regard this as an instance of the junction tree theorem [27, 28]. I report here the basic steps of a proof for the present case.

First of all, write the Hamiltonian as a sum of row-to-row terms:

\[
H(m) = \sum_{j=1}^{N-1} H_{j,j+1}(m_j, m_{j+1}).
\]  
(7)

If the Hamiltonian has the form reported in equation (5), then one can write

\[
H_{j,j+1} = b_j \sum_{i=1}^{j} h_{i,j} m_{i,j} + b_{j+1} \sum_{i=1}^{j+1} h_{i,j+1} m_{i,j+1,i} + \lambda \sum_{i=1}^{j} (m_{j+1,i} - m_{i,j} m_{j+1,i+1})^2,
\]  
(8)

where, in order to take into account the boundaries, \(b_1 = b_N = 1\) and \(b_j = 1/2\) for \(1 < j < N\). For simplicity of notation, I drop from now on the arguments of \(H_{j,j+1}\). Of course, the specific form of \(H_{j,j+1}\) is irrelevant here; only the splitting into terms involving only adjacent rows is important.

Then we introduce the Boltzmann distribution

\[
p(m) = \frac{1}{Z} \exp(-H) = \frac{1}{Z} \exp(-H_{1,2} \cdots - H_{N-1,N}),
\]  
(9)

where we have absorbed \(\beta = (k_B T)^{-1}\) in the definition of the Hamiltonian and introduced the partition function

\[
Z = \sum_m \exp(-H) = \sum_m \exp(-H_{1,2} \cdots - H_{N-1,N}).
\]  
(10)

Finally we define the marginal probability distributions for a row

\[
p_j(m_j) = \sum_{\{m_l, l \neq j\}} p(m), \quad 1 \leq j \leq N,
\]  
(11)

and for a pair of adjacent rows

\[
p_{j,j+1}(m_j, m_{j+1}) = \sum_{\{m_l, l \neq j, j+1\}} p(m), \quad 1 \leq j \leq N - 1.
\]  
(12)

The arguments of these probability will also be dropped in the following.

Introducing the partial partition functions for upper and lower portions of the lattice

\[
Z_{U,j}(m_j) = \sum_{m_{j-1}} \exp(-H_{j-1,j}) \cdots \sum_{m_1} \exp(-H_{1,2}),
\]

\[
Z_{L,j}(m_j) = \sum_{m_{j+1}} \exp(-H_{j,j+1}) \cdots \sum_{m_N} \exp(-H_{N-1,N}),
\]  
(13)

and together with the boundary conditions

\[
Z_{U,1}(m_1) = 1,
\]

\[
Z_{L,N}(m_N) = 1.
\]  
(14)

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it is easy to show that
\[ p_j = \frac{1}{Z} Z_{U,j}(m_j) Z_{L,j}(m_j), \]
\[ p_{j,j+1} = \frac{1}{Z} Z_{U,j}(m_j) Z_{L,j+1}(m_{j+1}) \exp(-H_{j,j+1}), \]
and hence
\[ \frac{p_{1,2} \cdots p_{N-1,N}}{p_2 \cdots p_{N-1}} = \frac{1}{Z} \exp(-H) = p(m). \]

This shows that the global probability can be written as a product of row-pair and row probabilities, raised to exponents 1 and \(-1\) respectively, which is the first step towards our final result. As a consequence, a CVM with all row-pairs as maximal clusters (see section 5) would be exact for this model, but this is not interesting here, since a much stronger property will be proved below.

The above discussion is not specific to the present model and so far the constraints have not yet been exploited. The next step is then to make use of the constraints to write the row and row-pair probabilities in a factor form similar to equation (16).

Consider first the row probability. Observe that, due to the constraints equation (4),
\[ m_{j,i} = 0 \Rightarrow m_{j,k} = 0 \quad \forall k < i, \]
\[ m_{j,i} = 1 \Rightarrow m_{j,k} = 1 \quad \forall k > i, \]
and the probability of the state \( e^k_j \) defined in equation (6) reduces to an NN pair probability:
\[ p_j(e^k_j) = p_{j,k+1}^{j,k+1}(0,1), \quad 1 \leq k < j \]
where \( p_{j,k+1}^{j,k+1}(m_{j,k}, m_{j,k+1}) \) is the NN (horizontal) pair probability for the pair at row \( j \) and columns \( k, k+1 \). Indeed, \( e^k_j \) is the only state of row \( j \) with \( m_{j,k} = 0 \) and \( m_{j,k+1} = 1 \).

In addition, for the states \( e^0_j \) (all 1s) and \( e^j_j \) (all 0s) one can write
\[ p_j(e^0_j) = p_{j}^{j,j+1}(1,1), \]
\[ p_j(e^j_j) = p_{j,j+1}^{j-1,j}(0,0) \]
(actually the probabilities for these states could be reduced to site probabilities, but this is not useful here).

Introducing the site probabilities \( p_j^{i,i+1}(m_{j,i}) \) and observing that
\[ p_j^{i,i+1}(0,0) = p_j^{i+1}(0), \]
\[ p_j^{i,i+1}(1,1) = p_j^{i}(1), \]
one can write the above results for the row probability in the \( k \)-independent factorized form
\[ p_j(e^k_j) = \frac{p_j^{1,2}(m_{j,1}, m_{j,2}) \cdots p_j^{j-1,j}(m_{j,j-1}, m_{j,j})}{p_j^{2}(m_{j,2}) \cdots p_j^{j-1}(m_{j,j-1})}. \]

A similar result can be obtained for the row-pair probability. In this case one needs to define the square probability \( p_{j,j+1}^{i,i+1}(m_{j,i}, m_{j,i+1}; m_{j+1,i}, m_{j+1,i+1}) \), the triangle probability
$p_{j,j+1}^{i,j+1}(m_{j}; m_{j+1,j}, m_{j+1,j+1})$ for the triangles lying on the diagonal boundary and the NN (vertical) pair probability $p_{j,j+1}^{i,i}(m_{j}; m_{j+1,i})$.

There are two kinds of row-pair configuration: $(e_j^k, e_{j+1}^k)$ which represents the cases in which peptidic bonds $j$ and $j+1$ are in the same native stretch (e.g. rows 3 and 4 in figure 1) or (for $k = j$) a new native stretch starts at $j+1$ (e.g. rows 7 and 8 in figure 1), and $(e_j^k, e_{j+1}^{j+1})$ which represents the cases in which a native stretch of length $j - k$ ends at $j$ (e.g. rows 5 and 6 in figure 1). For both kinds we have to show that a factorization like equation (21) occurs.

The proof parallels the one for the row probability. Consider the first kind of configuration and observe that, due to the constraints,

$$p_{j,j+1}(e_j^k, e_{j+1}^k) = p_{j,j+1}^{k,k+1}(0, 0; 0, 1), \quad 1 \leq k < j.$$  \hfill (22)

For the boundary cases one has

$$
p_{j,j+1}(e_j^0, e_{j+1}^0) = p_{j,j+1}^{1,2}(1, 1; 1, 1),
\quad p_{j,j+1}(e_j^j, e_{j+1}^0) = p_{j,j+1}^{j,j+1}(0, 0; 0, 1).
$$  \hfill (23)

Observing that

$$p_{j,j+1}^{i+1,j+1}(0; 0, 0) = p_{j,j+1}^{i+1,j+1}(0; 0)
\quad p_{j,j+1}^{i+1,j+1}(1, 1; 1, 1) = p_{j,j+1}^{i+1,j+1}(1; 1)$$

the row-pair probability can be written as

$$p_{j,j+1}(e_j^k, e_{j+1}^k) = \frac{p_{j,j+1}^{1,2} \cdots p_{j,j+1}^{j-1,j} p_{j,j+1}^{j,j+1}}{p_{j,j+1}^{1} \cdots p_{j,j+1}^{j}} \quad 0 \leq k \leq j,$$

where the last factor in the numerator is a triangle probability. For simplicity, the arguments of the probability have been dropped.

Consider now configurations of the second kind. Equations (22), (23) and (25) are replaced by

$$p_{j,j+1}(e_j^k, e_{j+1}^{j+1}) = p_{j,j+1}^{k,k+1}(0, 0; 0, 0), \quad 1 \leq k < j,$$  \hfill (26)

$$p_{j,j+1}(e_j^0, e_{j+1}^{j+1}) = p_{j,j+1}^{1,2}(1, 1; 0, 0),
\quad p_{j,j+1}(e_j^j, e_{j+1}^{j+1}) = p_{j,j+1}^{j,j+1}(0, 0; 0, 0)$$

and

$$p_{j,j+1}(e_j^k, e_{j+1}^{j+1}) = \frac{p_{j,j+1}^{1,2} \cdots p_{j,j+1}^{j-1,j} p_{j,j+1}^{j,j+1}}{p_{j,j+1}^{1} \cdots p_{j,j+1}^{j}} \quad 0 \leq k \leq j,$$

respectively.

The factorization property

$$p_{j,j+1}(m_j, m_{j+1}) = \frac{p_{j,j+1}^{1,2} \cdots p_{j,j+1}^{j-1,j} p_{j,j+1}^{j,j+1}}{p_{j,j+1}^{2} \cdots p_{j,j+1}^{j}} \quad 0 \leq k \leq j$$

is then proved for any valid row-pair configuration.

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In order to obtain the final result of this section, plug equations (21) and (29) into equation (16), obtaining

\[ p(m) = \frac{\left( \prod_{j=1}^{N-1} \prod_{i=1}^{j} p_{i,j+1}^{i+1} \right) \left( \prod_{j=3}^{N-1} \prod_{i=2}^{j-1} p_{i,j+1}^{i+1} \right)}{\left( \prod_{j=2}^{N-1} \prod_{i=2}^{j} p_{i,j+1}^{i+1} \right) \left( \prod_{j=2}^{N-1} \prod_{i=1}^{j-2} p_{i,j+1}^{i+1} \right)}, \]

that is the global probability is reduced to a product of square, triangle and site probabilities divided by a product of pair probabilities.

5. Exactness of the cluster variation method

In this section, after a brief introduction to the CVM, it is shown that the factorization equation (30) implies the exactness of the CVM, and the consequences of this property are discussed.

The CVM in its modern formulation is derived from the variational principle of statistical mechanics, which states that, given a model with variables \( m \) and Hamiltonian \( H(m) \), its equilibrium (Boltzmann) probability distribution \( p_{eq}(m) = \exp(-H(m))/Z \) is the distribution which minimizes the variational free energy

\[ F = U - S = \sum_m p(m)H(m) + \sum_m p(m) \ln p(m). \]

The physical values of the free energy \( F \), the energy \( U \) and the entropy \( S \) can then be calculated at the minimum.

If the variables are associated to the nodes of a graph, or to the sites of a lattice, one can define clusters of nodes (e.g. single sites, pairs, triangles, square plaquettes, ...). For each cluster \( \alpha \) define also the corresponding set of variables \( m_{\alpha} \), probability distribution \( p_{\alpha}(m_{\alpha}) \) and entropy

\[ S_{\alpha} = -\sum_{m_{\alpha}} p_{\alpha}(m_{\alpha}) \ln p_{\alpha}(m_{\alpha}). \]

The entropy cumulants are defined by

\[ S_{\alpha} = \sum_{\beta \subseteq \alpha} \tilde{S}_{\beta}, \]

which can be solved with respect to the cumulants by means of a Möbius inversion, which yields

\[ \tilde{S}_{\beta} = \sum_{\alpha \subseteq \beta} (-1)^{n_{\alpha} - n_{\beta}} S_{\alpha}, \]

where \( n_{\alpha} \) denotes the number of nodes in cluster \( \alpha \).

The full entropy

\[ S = \sum_{\beta} \tilde{S}_{\beta} \]

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can then be approximated by selecting a set $R$ of clusters, made of certain maximal clusters and all their subclusters, and truncating the cumulant expansion by retaining only terms which correspond to clusters in $R$. One obtains

$$S \simeq \sum_{\beta \in R} \tilde{S}_{\beta} = \sum_{\alpha \in R} a_{\alpha} S_{\alpha},$$  

(36)

where the coefficients $a_{\alpha}$, sometimes called Möbius numbers, satisfy

$$\sum_{\alpha \in R, \alpha \supseteq \beta} a_{\alpha} = 1 \quad \forall \beta \in R.$$  

(37)

The above condition, practically useful for determining the $a_{\alpha}$s, means that every subcluster must be counted exactly once in the entropy expansion.

Now assume that the Hamiltonian is made of local terms only, and $R$ has been chosen such that one can write

$$H(m) = \sum_{\alpha \in R} H_{\alpha}(m_{\alpha}).$$  

(38)

In such a case the variational free energy can be written, with the above approximation on the entropy and no approximation on the energy, as

$$F_{\text{CVM}} = \sum_{\alpha \in R} \sum_{m_{\alpha}} p_{\alpha}(m_{\alpha}) H_{\alpha}(m_{\alpha}) + \sum_{\alpha \in R} a_{\alpha} \sum_{m_{\alpha}} p(m_{\alpha}) \ln p(m_{\alpha}),$$  

(39)

where the minimization must be performed with respect to the $p_{\alpha}$s with the constraints

$$\sum_{m_{\alpha}} p_{\alpha}(m_{\alpha}) = 1, \quad \forall \alpha \in R,$$

$$\sum_{m_{\alpha} \setminus \beta} p_{\alpha}(m_{\alpha}) = p_{\beta}(m_{\beta}), \quad \forall \beta \subset \alpha \in R.$$  

(40)

It is interesting to observe that a suitable factorization of the equilibrium probability of the model implies that the variational free energy equation (31) reduces to the CVM variational free energy equation (39) with no approximation. More precisely, assume that the equilibrium probability factorizes in terms of its marginals according to

$$p_{\text{eq}}(m) = \prod_{\alpha \in R} [p_{\alpha}(m_{\alpha})]^{a_{\alpha}}.$$  

(41)

Then one can restrict the variational principle to distributions $p(m)$ with the same property. The entropy of such a distribution is

$$S = -\sum_{m} p(m) \ln p(m)$$

$$= -\sum_{\alpha} a_{\alpha} \sum_{m} p(m) \ln p_{\alpha}(m_{\alpha})$$

$$= -\sum_{\alpha} a_{\alpha} \sum_{m_{\alpha}} p_{\alpha}(m_{\alpha}) \ln p_{\alpha}(m_{\alpha}),$$  

(42)

and the CVM free energy is therefore obtained with no approximation (recall that no approximation was made on the energy term).
The WSME model in its two-dimensional representation falls precisely in this case. If one chooses as maximal clusters all the square plaquettes and the triangles lying on the diagonal boundary, the Hamiltonian can obviously be written as in equation (38) and the Möbius numbers for the entropy expansion, obtained by equation (37), are:

- $a_\alpha = 1$ for the maximal clusters;
- $a_\alpha = 0$ for the triangles not lying on the diagonal boundary and the next-nearest-neighbour pairs, since they are contained in exactly 1 maximal cluster;
- $a_\alpha = -1$ for all the NN pairs contained in two maximal clusters, that is all NN pairs except the boundary ones;
- $a_\alpha = 0$ for the boundary NN pairs;
- $a_\alpha = 1$ for the sites contained in four maximal clusters and four NN pairs, that is all sites except the boundary ones;
- $a_\alpha = 0$ for the boundary sites.

With the above Möbius numbers it is immediate to check that the factorization equation (41) is exactly the one that we have obtained in equation (30) for the WSME model, and hence the CVM is exact for this model. The corresponding variational free energy, dropping all the arguments in the entropy term, reads

$$
F = \sum_{j=1}^{N} \sum_{i=1}^{j} h_{i,j} \sum_{m_{j,i}} m_{j,i} p_j^i(m_{j,i}) + \sum_{j=1}^{N-1} \sum_{i=1}^{j} p_{j,j+1}^{i,i+1} \ln p_{j,j+1}^{i,i+1}
- \sum_{j=2}^{N-1} \sum_{i=2}^{j-1} p_{j,j+1}^{i,i+1} \ln p_{j,j+1}^{i,i+1} - \sum_{j=2}^{N-1} \sum_{i=1}^{j-1} p_{j}^{i,i+1} \ln p_{j}^{i,i+1}
+ \sum_{j=3}^{N-1} \sum_{i=2}^{j-1} p_{j}^{i,i+1} \ln p_{j}^{i,i+1}
$$

(43)

The local constraints equation (4) can either be included in the Hamiltonian or imposed by hand on the probabilities.

The numerical minimization of the above variational free energy can in principle be performed by a provably convergent, double-loop algorithm like the one proposed by Heskes et al [29], while the GBP fails, probably due to the constraints, except in very simple cases. This is not an important point, however, since the strength of this result is not that it improves on the transfer matrix method, which is already very efficient in solving for the equilibrium. Hence the only advantage of this approach is probably that in this scheme it is easier to calculate correlation functions, since the probabilities are directly accessible.

The real strength of this result, apart from having found a new model which is exactly solvable by the CVM, is that here the CVM can serve as a basis to build a powerful approximation for the dynamics of the model, which is extremely relevant for the protein folding problem. For this purpose, it might also be useful to observe that the variational free energy can be written explicitly in terms of the local expectations

$$
x_{j,i} = \langle m_{j,i} \rangle = \sum_{m_{j,i}=0,1} m_{j,i} p_j^i(m_{j,i}) = p_j^i(1).
$$

(44)
To this end observe that in the variational free energy equation (43) the energy term is already a linear function of these expectations, while the probabilities appearing in the entropy term can be written as functions of these expectations as independent variables. For instance, using equation (44) and normalization one obtains

$$
\begin{align*}
p_j^i(1) &= x_{j,i} \\
p_j^i(0) &= 1 - x_{j,i}.
\end{align*}
$$

(45)

For the NN pair one configuration is forbidden by the constraints, and the remaining probabilities are determined by normalization and marginalization to the site probabilities, obtaining

$$
\begin{align*}
p_j^{i,i+1}(0, 0) &= 1 - x_{j,i+1} \\
p_j^{i,i+1}(0, 1) &= x_{j,i+1} - x_{j,i} \\
p_j^{i,i+1}(1, 1) &= x_{j,i}
\end{align*}
$$

(46)

for the horizontal pair and

$$
\begin{align*}
p_j^{i,j+1}(0, 0) &= 1 - x_{j,i} \\
p_j^{i,j+1}(1, 0) &= x_{j,i} - x_{j+1,i} \\
p_j^{i,j+1}(1, 1) &= x_{j+1,i}
\end{align*}
$$

(47)

for the vertical pair. Similarly, for a triangle lying on the diagonal boundary, only four configurations are allowed by the constraints, and their probabilities are again determined by normalization and marginalization to subclusters, with the result

$$
\begin{align*}
p_j^{i,i+1}(0; 0, 0) &= 1 - x_{j,i} - x_{j+1,i} + x_{j+1,i} \\
p_j^{i,i+1}(0; 0, 1) &= x_{j+1,i} - x_{j+1,i} \\
p_j^{i,i+1}(1; 0, 0) &= x_{j,i} - x_{j+1,i} \\
p_j^{i,i+1}(1; 1, 1) &= x_{j+1,i}.
\end{align*}
$$

(48)

Finally, for a square plaquette we have five allowed configurations and the probabilities

$$
\begin{align*}
p_j^{i,i+1}(0, 0; 0, 0) &= 1 - x_{j,i+1} \\
p_j^{i,i+1}(0, 1; 0, 0) &= x_{j,i+1} + x_{j+1,i} - x_{j,i} - x_{j+1,i+1} \\
p_j^{i,i+1}(0, 1; 0, 1) &= x_{j+1,i+1} - x_{j+1,i} \\
p_j^{i,i+1}(1, 1; 0, 0) &= x_{j,i} - x_{j+1,i} \\
p_j^{i,i+1}(1, 1; 1, 1) &= x_{j+1,i}.
\end{align*}
$$

(49)

Substituting the above probabilities into the variational free energy equation (43) yields an exact variational free energy as a function of $N(N+1)/2$ independent local variables.
6. Conclusions

I have shown that the equilibrium probability factors into a product of local cluster probabilities, and hence the CVM is exact, for the WSME model of protein folding. After the one-dimensional WSME model, which has long-range, many-body interactions, has been mapped into a two-dimensional model which has local constraints as the only interactions, the proof goes through two steps. The first step exploits the locality of the interactions, the second one the detailed form of the constraints.

The result is especially relevant on the methodological side, since leaving apart treelike models, the CVM is exact, as far as I know, only on disorder varieties of two-dimensional models.

Moreover, some consequences can also be expected on the model side. As far as equilibrium properties are concerned, we have almost no improvement with respect to the transfer matrix method, which is already very fast in this matter. The main advantage of the CVM solution is that correlation functions are much easier to calculate. The most important point is, however, that the CVM solution for the equilibrium can be a starting point for good approximations for the dynamics, which is of utmost importance in the context of the protein folding problem. Two approaches can be followed [30, 31]. On the one hand, one can develop a master equation approach based on the approximation that the state of the system at any time can be described as an equilibrium state of the WSME model, with a time-dependent Hamiltonian (the so-called local equilibrium approximation [32]). On the basis of the results reported here, this means that the probability at any time is assumed to factorize as the equilibrium one. Alternatively, one can build an approximation for the dynamics with the path probability method (PPM, the dynamical version of the CVM) [7], with square plaquettes and triangles as maximal clusters. Since the stationary state of the PPM corresponds to the CVM solution for the equilibrium, one obtains an approximation for the dynamics which is guaranteed to converge to the exact equilibrium state. It can be verified [30, 31] that the two approaches are equivalent in the limit of vanishing time step and that very good agreement is obtained with respect to the exact solution for short chains.

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