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# Folding and Design in Coarse-Grained Protein Models

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Recent advances in coarse-grained lattice and off-lattice protein models are reviewed. The sequence dependence of thermodynamical folding properties are investigated and evidence for non-randomness of the binary sequences of good folders are discussed. Similar patterns for non-randomness are found for real proteins. Dynamical parameter MC methods, such as the tempering and multisequence algorithms, are essential in order to obtain these results. Also, a new MC method for design, the inverse of folding, is presented. Here, one maximizes conditional probabilities rather than minimizing energies. By construction, this method ensures that the designed sequences represent good folders thermodynamically.

## 1. Introduction

Proteins are heterogenuous chain molecules composed of sequences of amino acids. The protein folding problem amounts to given a sequence of amino acids predict the protein 3D structure. There are 20 different amino acids. In the *Bioinformatics* approach one aims at extracting rules in a "black-box" manner by relating sequence with structure from databases. Here we pursue the physics approach, where given interaction energies, the 3D structures and their thermodynamical properties are probed. In principle, this can be pursued on different levels of resolution. *Ab initio* quantum chemistry calculations can not handle the huge degrees of freedom, but are of course useful for estimating interatomic potentials. All-atom representations, where the atoms are the building blocks, also require very large computing resources for the full folding problem including thermodynamics, but are profitable for computing partial problems, binding energies etc.

Here we pursue a course-grained representation, where the entities are the amino acids. This is motivated by the fact that the hydrophobic properties of the amino acids play a most important role in the folding process – the amino acids that are hydrophobic (H) tend to form a core, whereas the hydrophilic or polar ones (P) are attracted to the surrounding $H_2O$ solution. In such representations, the interactions between the amino acids and the solvent are reformulated in an *effective interaction* between the amino acids.

## 2. Coarse-Grained Models

Both lattice and off-lattice models have here been studied.

A well studied lattice model is the HP model [1]

$$E(r,\sigma) = -\sum_{i<j} \sigma_i \sigma_j \Delta(r_i - r_j) \qquad (1)$$

where $\Delta(r_i - r_j) = 1$ if monomers $i$ and $j$ are non-bonded nearest neighbors and 0 otherwise. For hydrophobic and polar monomers, one has $\sigma_i = 1$ and 0, respectively. Being discrete, this model has the advantage that for sizes up to $N = 18$ in 2D it can be solved exactly by exhaustive enumeration.

Similarly off-lattice models have been developed, where adjacent residues are linked by rigid bonds of unit length to form linear chains [2,3]. The energy function is given by

$$E(r,\sigma) = \sum_i F_i + \sum_{i<j} \epsilon(\sigma_i, \sigma_j)[r_{ij}^{-12} - r_{ij}^{-6}] \quad (2)$$

where $F_i$ is a local sequence-independent interaction chosen to mimic the observed local correlations among real proteins and the second term corresponds to amino-acid interactions, the strengths/signs of which are governed by $\epsilon(\sigma_i, \sigma_j)$.

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## 3. Folding

Investigating thermodynamical properties of chains given by Eqs. (1,2) is extremely tedious with standard MC methods; Metropolis, the hybrid method etc. Hence novel approaches are called for. *Dynamical Parameter* approaches have here turned out to be very powerful; the *tempering* [4,5] and *multisequence* [6] methods. In both approaches one enlarges the Gibbs distribution. In [4,5] one simulates

$$P(r,k) = \frac{1}{Z}\exp(-g_k - E(r,\sigma)/T_k) \qquad (3)$$

with ordinary $r$ and $k$ updates for $T_1 < \ldots < T_K$, regularly quenching the system to the ground state. The weights are $g_k$ are chosen such that the probability of visiting the different $T_k$ is roughly constant. Similarly in the multisequence method the degrees of freedom are enlarged to include different sequences according to

$$P(r,\sigma) = \frac{1}{Z}\exp(-g_\sigma - E(r,\sigma)/T) \qquad (4)$$

where again $g_\sigma$ is a set of tunable parameters, which are subject to moves jointly with $r$.

When estimating thermodynamical quantities, these dynamical parameter methods yield speedup factors of several orders of magnitude.

A key issue when studying properties of protein models are to what extent different sequences yield structures with good folding properties from a thermodynamic standpoint. Defining good folding properties is straightforward in the lattice model case – non-degenerate ground states. For off-lattice models a suitable measure can be defined in terms of the mean-square distance $\delta^2_{ab}$ between two arbitrary configurations $a$ and $b$. An informative measure of stability is the mean $\langle\delta^2\rangle$ [7]. With a suitable cut on $\langle\delta^2\rangle$ good folders are singled out. For both lattice and off-lattice models, only a few % of the sequences have good folding properties [1]. When analyzing the sequence properties of good folders, one finds that similar signatures occur among real proteins when using a binary coding for the hydrophobicities [8]. One might speculate that only those sequences with good folding properties survived the evolution.

[1] Similar fractions are obtained within the replica approach for lattice models [9].

## 4. Design

The "inverse" of protein folding, sequence optimization, is of utmost relevance in the context of drug design. Here, one aims at finding optimal amino acid sequences given a target structure such that the solution represents a good folder. This corresponds to maximizing the conditional probability [10],

$$P(r_0|\sigma) = \frac{1}{Z(\sigma)}\exp(-E(r_0,\sigma)/T) \qquad (5)$$

$$Z(\sigma) = \sum_r \exp(-E(r,\sigma)/T) \qquad (6)$$

Note that here $Z(\sigma)$ is not a constant quantity. A straightforward approach would therefore require a nested MC – for each step in $\sigma$ a complete MC has to be performed in $r$ [11]. Needless to say, this is extremely time consuming. Various approximations for $Z$ has been suggested; chemical potentials fixing the net hydrophobicity and low-$T$ expansions [12]. Neither of these produce good folders in a reliable way.

Here we devise a different strategy based upon the multisequence method [13]. The starting point is the joint probability distribution (Eq. (4)) The corresponding marginal distribution is given by

$$\begin{aligned} P(\sigma) &= \sum_r P(r,\sigma) = \frac{1}{Z}\exp(-g_\sigma)Z(\sigma) \\ Z &= \sum_\sigma \exp(-g_\sigma)Z(\sigma) \end{aligned} \qquad (7)$$

With the choice

$$g_\sigma = -E(r_0,\sigma)/T \qquad (8)$$

one obtains

$$P(r_0|\sigma) = \frac{P(r_0,\sigma)}{P(\sigma)} = \frac{1}{ZP(\sigma)} \qquad (9)$$

In other words, maximizing $P(r_0|\sigma)$ is in this case equivalent to minimizing $P(\sigma)$. This implies that bad sequences are visited more frequently than

good ones in the simulation. This property may seem strange at a first glance. However, it can be used to eliminate bad sequences. The situation is illustrated in Fig. 1. Basically, one runs a

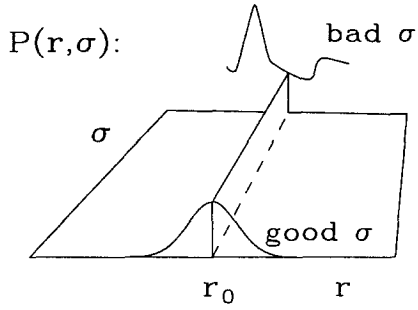


Figure 1. The distribution $P(r,\sigma)$. The choice of $g_\sigma$ (Eq. (8)) implies that $P(r_0,\sigma)$ is flat in $\sigma$. Sequences not designing $r_0$ have maxima in $P(r_i|\sigma)$ for $r_i \neq r_0$ due to states with $E(r_i,\sigma) \leq E(r_0,\sigma)$. Sequence designing $r_0$ have unique maxima at $r = r_0$ in $P(r|\sigma)$, which for low $T$ contains most of the probability.

MC in both $r$ and $\sigma$ using all (or a subset of) the sequences. Regularly, one estimates $P(\sigma)$. Sequences where $P(\sigma)$ exceeds a certain threshold are then eliminated, thereby purifying the sample towards designing sequences according to Eq. (9). For lattice models one can use an alternative to eliminating high $P(\sigma)$ sequences, by removing sequences with $E(r,\sigma) \leq E(r_0,\sigma)$.

Testing any design algorithm requires that one has access to *designable* structures, i.e. structures for which there exist good folding sequences. Furthermore, after the design process, it must be verified that the designed sequence indeed has the structure as a stable minimum (good folder). For $N \leq 18$ 2D lattice models this is of course feasible, since these models can be enumerated exactly. For larger lattice models and off-lattice models this is not the case and testing the design approach is more laborious.

Extensive tests have been performed for $N$=16, 18, 32 and 50 lattice and $N$=16 and 20 off-lattice chains respectively. For systems exceeding $N$=20 one cannot go through all possible sequences. Hence a bootstrap procedure has been devised, where a set of preliminary runs with subsets of sequences is first performed. Positions along the chain with clear assignments of H or P are then clamped and the remaining degrees of freedom are run with all sequences visited. With no exceptions, the design algorithm efficiently singles out sequences that folds well into the (designable) target structures.

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