An Inverse Equilibrium Maximum Entropy Algorithm
Applied To Proteins
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Abstract
A computational method is developed to work on an inverse equilibrium problem with an interest towards applications with protein folding. In general, we are given a set of equilibrium configurations, and want to derive the most likely potential function that results in these configurations. The method is applied to polymer simulations and a simple model of proteins using protein structures obtained from the Protein Data Bank (http://www.rcsb.org/pdb). The resulting energy function is tested on a few decoy sets with limited success.

Introduction
The Protein Data Bank (http://www.rcsb.org/pdb) has about 19,000 protein structures solved by several methods. There are many algorithms that use this information to derive understanding about protein interactions. Our method is based on using these equilibrium configurations and a maximum entropy algorithm to derive information about physical energy functions that could be used to approximate protein interactions.

Our Method
The following is based largely on an algorithm originally developed by reference [5]. The method is based on the following assumptions. The system is assumed to be in thermodynamic equilibrium. For proteins, this was shown to be a good assumption by Anfinsen [1]. We also assume the energy can be written as a sum of terms which are products of parameters and functions of the configuration.

\[ E(\Gamma, \vec{P}) = \sum_i p_i h_i(\Gamma) = \vec{P} \cdot \vec{H} \]

where \( \Gamma \) represents the configuration of the system(s). \( \vec{P} = \{p_i\} \) represents the set of parameters to be derived.

The probability of a configuration, given parameters, is given by the Boltzmann distribution

\[ P(\Gamma|\vec{P}) = e^{-E(\Gamma, \vec{P})/kT} / Z = e^{(-E(\Gamma, \vec{P})+F(\vec{P}))/kT} \]

where \( Z(\vec{P}) = \sum_{\Gamma} \exp(-\beta E(\Gamma, \vec{P})) \) and \( F(\vec{P}) = -kT \ln(Z(\vec{P})) \).

If we are given the exact equilibrium conformation, \( \Gamma^* \), the maximum likelihood of parameter values are those values for which the probability, \( P(\Gamma^*|\vec{P}) \) is a maximum wrt \( \vec{P} \). Maximizing an exponential corresponds to maximizing the argument (ignoring the multiplicative constant \( \beta \)), \( -E(\Gamma^*, \vec{P}) + F(\vec{P}) = Q(\vec{P}) \).

This also corresponds to extremizing the entropy \( TS = E - F \).

Our method is basically the multi-dimensional form of Newton’s method for optimizing functions. Maximizing \( Q(\vec{P}) \), Newton’s Method is

\[ \vec{P}^{k+1} = \vec{P}^k - D^2(Q(\vec{P}^k))^{-1} \cdot D(Q(\vec{P}^k)) \]  

(1)
where \((D^2)^{-1}\) represents the inverse Hessian matrix and D represents the gradient. In practice this is modified slightly,

\[
\vec{P}_{k+1} = \vec{P}_k + \epsilon (\Delta \vec{P})
\]

where the use of \(\epsilon < 1\) corresponds to the "Damped Newton’s Method".

Using statistical mechanical definitions

\[
\frac{\partial (-E(\Gamma^*))}{\partial p_i} = -h_i^* \\
\frac{\partial^2 (-E(\Gamma^*))}{\partial p_i \partial p_j} = 0
\]

\[
\frac{\partial F}{\partial P_i} = -kT \sum \beta h_i e^{-\beta E(\Gamma, P)} = < h_i >
\]

\[
\frac{\partial^2 F}{\partial p_i \partial p_j} = \beta (< h_i > < h_j > - < h_i h_j >)
\]

Maximizing \(Q = -E + F\) wrt \(\vec{P}\) leads to the following.

\[
D(Q)_i = -h_i^* + < h_i >
\]

\[
D^2(Q)_{i,j} = \beta(< h_i > < h_j > - < h_i h_j >) = -\beta Cov(h_i, h_j)
\]

Resulting in the following iterative equation where \(V CM(\vec{H})\) is the variance-covariance matrix of \(\vec{H}\)

\[
\Delta \vec{P} = kT \cdot V CM(\vec{H})^{-1} \cdot (< \vec{H} > - \vec{H}^*)
\]

The method is easily generalized to a distribution of equilibrium configurations.

\[
\Delta \vec{P} = kT \cdot V CM(\vec{H})^{-1} \cdot (< \vec{H} > - < \vec{H} >_{prob(\Gamma)})
\]

\(< ... >\) represents a Boltzmann average and \(< ... >_{prob(\Gamma)}\) represents an average over the given distribution.

Assuming the least prior information, the iteration starts with all parameters set to zero. This would not allow any useful MC evolution at all. The energy would be zero for any Monte Carlo move, thus not preferring any particular move. The energy is modified for the first few iterations with the addition of a clamping term.

\[
E_{clamp} = \sum P_{clamp} \cdot (r - r^*)^2
\]

This term makes the given conformation a minimum of the energy. Since this conformation is an equilibrium conformation, this seems to be a good approximation. Once the parameter values are sufficiently away from zero, this term is set to zero. If a distribution of conformations is given, this distribution can be used as the clamping terms.
Computation

The basic algorithm is as follows.

- Given $P^k$, Monte Carlo simulations and averaging are used to find $< h_j >$ and $< h_i h_j >$.
- This leads to a matrix equation. $\Delta \vec{P} = kT \ast VCM(\vec{H})^{-1} \ast ( < \vec{H} > - \vec{H}^* )$
- Solve this for $\Delta \vec{P}$
- $\vec{P}^{k+1} = \vec{P}^k + \epsilon(\Delta \vec{P})$
- Repeat until $\vec{P}$ converges.

Computation: Convergence time

Assuming a system of $M$ proteins, each containing $N$ particles with $P$ parameters. The Monte Carlo time required for useful averaging scales at least as $N^3$. The pair-wise energy calculation in each Monte Carlo step scales as $N^2$. Although for some models a radius cutoff and neighbor list were used, so this effect in practice is less than indicated. Solving a $P$ by $P$ matrix equation is a $P^3$ operation. Computation time for this method scales as

\[ \alpha M \ast N^3 + \beta P^3 \]  

(11)

Simulation

A Monte Carlo evolution was done on several systems. Four energy terms were used.

\[ \pm \frac{a}{|r_i - r_j|} + \frac{b}{(r_i - r_j)^{12}} + c \ast |r_i - r_{i+1}| + d \ast (r_i - r_{i+1})^2 \]  

(12)

Non-bonded interactions were included similar to an electrostatic attraction and van der Waals repulsion. The sequence of positive and negative charges was randomly chosen. A covalent-type bond between one particle and the next in the sequence was given a quadratic form. For the simulation described below, the following parameters were used $a = 2, b = 4, c = -4, d = 1$. The results of the algorithm applied to this system are shown in figure 1 and table 1.
Figure 1: A collection of 99, 8 particle proteins was constructed with $a = 2, b = 4, c = -4, d = 1, kt = 0.25$ The algorithm used $\epsilon = 0.5$ and 120 MC moves per particle per iteration. Clamping was turned off at time=16 Using a computer with dual P3 450-667Mhz this took 1.5 hrs

| Correct Value | Derived value |
|---------------|---------------|
| 2             | $2.01 \pm 0.01$ |
| 4             | $4.36 \pm 0.03$ |
| $-4$          | $-3.88 \pm 0.03$ |
| 1             | $0.97 \pm 0.01$ |

Table 1: Parameters derived from equilibrium configurations compare well with correct values.
Protein Model

Several major simplifications were made to allow convergence of real protein parameters in a reasonable time. The united residue approximation is used in the following model. Each of the residues is treated as one particle. This approximation is commonly used [2, 6, 8]. This greatly simplifies the system, but should contain enough complexity to describe the system adequately.

Proteins seem to have a rugged free energy surface. To minimize this effect we use relatively few MC time steps per iteration. This keeps the protein in the local minimum of free energy even if parameters are far from correct.

Residues were placed at the $C_\alpha$ location, covalently bond only with next and previous particles on the chain. The energy function used for the covalent bonds was a normal distribution using the mean and variance derived from the data. The noise in the covalent bond parameter seemed to cause large perturbations in the convergence for other parameters. These parameters need to be derived separately.

The first model with consistent convergence used a statistical grouping of residues developed by Cieplak et al [4]. The groupings were derived using a simplification of a statistically derived interaction matrix, the Miyazawa Jernigan (MJ) matrix [9]. This is a simple, consistent grouping which decreases the number of parameters.

- Hydrophobic I (ave hydrophobic scale value 2.6) (LFI) Leucine, Isoleucine and Phenylalanine
- Hydrophobic II (ave HP scale value 1.8 with large variance) (MVWCY) Methionine, Valine, Tryptophan, Cysteine and Tyrosine
- Polar I (ave HP scale value 1.15) (HA) Histidine, Alanine
- Polar II (ave HP scale value 0.6) (TGPRQSNED) Threonine, Glycine, Proline, Arginine, Glutamine, Serine, Asparagine Glutamic acid and Aspartic acid
- Lysine (ave HP scale value 1.9) (K) Lysine

Only one energy term was used corresponding to van der Waals attraction

$$4\varepsilon[(\sigma/r)^{12} - (\sigma/r)^{6}]$$

Essentially this is a contact energy function. $\sigma$ was determined by comparing typical volumes and treating the residues as spheres. This gives radii from 2.4 - 3.8 Angstrom. $\sigma$ in the equation corresponds to where the core repulsion occurs (about 2*radius) so a value of 5 was arbitrarily assumed.

In summary, the covalent properties were approximated from the mean and variance of bond lengths. The energy function has one term, a 6-12 combined term. A statistical grouping was used to further reduce parameters. This grouping and energy function model has 15 parameters. Results shown below were
derived from proteins ranging in size from 20 to 400 residues. For consistency, only X-ray data and only complete proteins containing no extraneous molecules were used. The training set contained 821 proteins. All protein structures were obtained from the Protein Data Bank [3]. Only 20 MC steps per particle were used.

**Protein Models - Results**

Energy function: $4\epsilon[(\sigma/r)^{12} - (\sigma/r)^6]$ with $\sigma = 5$

| Group | Hydrophobic I | H II | Polar I | P II | Lysine |
|-------|---------------|------|---------|------|--------|
| H I   | 0.039         | 0.033| 0.039   | 0    | 0.015  |
| H II  | 0.042         | 0.042| 0       | 0.038|        |
| P I   | 0.033         | 0    | 0.036   |      |        |
| P II  | 0             |      | 0       | 0.018|        |
| Lysine|               |      |         |      | 0.020  |

Table 2: Attractive contact energy. Units are kT, $\sigma = 5$

The zeros were artificially created, as the algorithm can not handle these parameters going negative. ($\epsilon \geq 0$) This would cause the MC to diverge. Despite this limitation, convergence was achieved. These results imply the least hydrophobic (most polar) group essentially has no non-bonded interactions. This is very similar to the HP model of polymers where hydrophobic collapse is modeled as HH attraction and other interactions (HP and PP) are ignored. This took 14 days on a Dual PIII 450MHz.
Figure 2: Parameters vs Iteration time showing a distribution of variances in derived parameters
Protein Models - Model Evaluation

This energy function was applied to several decoy sets. Despite the simplicity of the energy function, results were mixed with several very encouraging successes. All decoy sets were obtained from [http://dd.stanford.edu/](http://dd.stanford.edu/)

### 4 State Reduced Decoy Set [10]

| Protein | Rank | Correct structure | ave energy | $\Delta/\sigma$ | present in data set? |
|---------|------|-------------------|------------|----------------|----------------------|
| 1ctf    | 1/631| 16.9              | 19.3       | 1.9            | n                    |
| 1r69    | 1/676| 8.7               | 9.9        | 1.5            | y                    |
| 1sn3    | 10/661| 16.3              | 18.1       | 1.3            | n                    |
| 2cro    | 1/675| 14.4              | 15.8       | 1.3            | n                    |
| 3icb    | 25/654| 14.6              | 15.5       | 0.9            | y                    |
| 4pti    | 574/688| 12.9              | 12.3       | -0.7           | y                    |
| 4rxn    | 347/678| 43.2              | 52.8       | 0.5            | y                    |

Table 3: Ranking of correct structure energy using our energy function using the 4state reduced decoy set from Park and Levitt, 1996 [10].

### Local Minima Decoy Set (lmds) [7]

Similar analysis was done for the lmds decoy set from C Kesar and M Levitt, 1999. These results were not very encouraging. The correct proteins were the worst scores in almost all cases and by a large amount. Currently the main weakness is due to the difference in deriviation for the covalent bonds. This decoy set was created using a minimization of a backbone torsional energy function, hence was very different from our function. Essentially, our successful decoy set predictions are based on only non-bonded interaction calculations.

### Fisa Casp3 Decoy Set [11]

| Protein | Rank | Correct structure | ave energy | $\Delta/\sigma$ | present in data set? |
|---------|------|-------------------|------------|----------------|----------------------|
| 1bl0    | 537/972| 17.6              | 18.9       | 0.2            | n                    |
| 1eh2    | 1/2414| 24.0              | 26.2       | 0.5            | n                    |
| 1bg8-A  | 1/1201| 16.3              | 17.1       | 0.3            | n                    |
| 1jwe    | 1/1408| 18.7              | 21.9       | 0.7            | n                    |
| 1smd3   | 226/1201| 12.4              | 13.3       | 0.5            | n                    |

Table 4: Ranking of correct structure energy using our energy function using fisa casp3 decoy set from Simons KT, et al, 1997 [11]. None were present in the data used in the derivation.
Protein Models - Discussion

The energy function used is extremely simple. Despite this, ranking of the native protein for some of the decoys was very encouraging. The poor performers probably need more complex energy functions. Correlation between RMDS and energy was investigated, but no simple relationship was found. For the best performers, the native energy was typically isolated at the lowest energy with most decoys concentrated a distinct difference in energy away.

The algorithm has potential, but several problems must be overcome. Complexity has not been handled very well and may be required for applicability. Inclusion of Coulomb, torsional, angular and backbone potential terms are required for realistic models. All atom and explicit solvent are further steps that can be taken. Terms of smaller magnitude are dominated by effects of terms with larger magnitude and have to be separately derived. Similarly, terms with smaller frequency of occurrence are dominated by more frequent terms. This separate derivation of terms can be organized and iterated consistently.

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