Long- and short-range interactions

in native protein structures

are consistent/minimally-frustrated in sequence space

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1. INTRODUCTION

A principle of consistency among various interactions in protein native structures

- It was proposed by Go (1983) from the fact that various prediction methods of protein secondary structure based solely on short-range interactions are fairly successful, even though long-range interactions are essential to fold protein structures,

- The consistency among interactions is an effective way for proteins to increase structural stabilities.

Consistent/Unfrustrated Enegy Landscape

Total energy

Interaction - A

Interaction - B

Energy

Conformational space
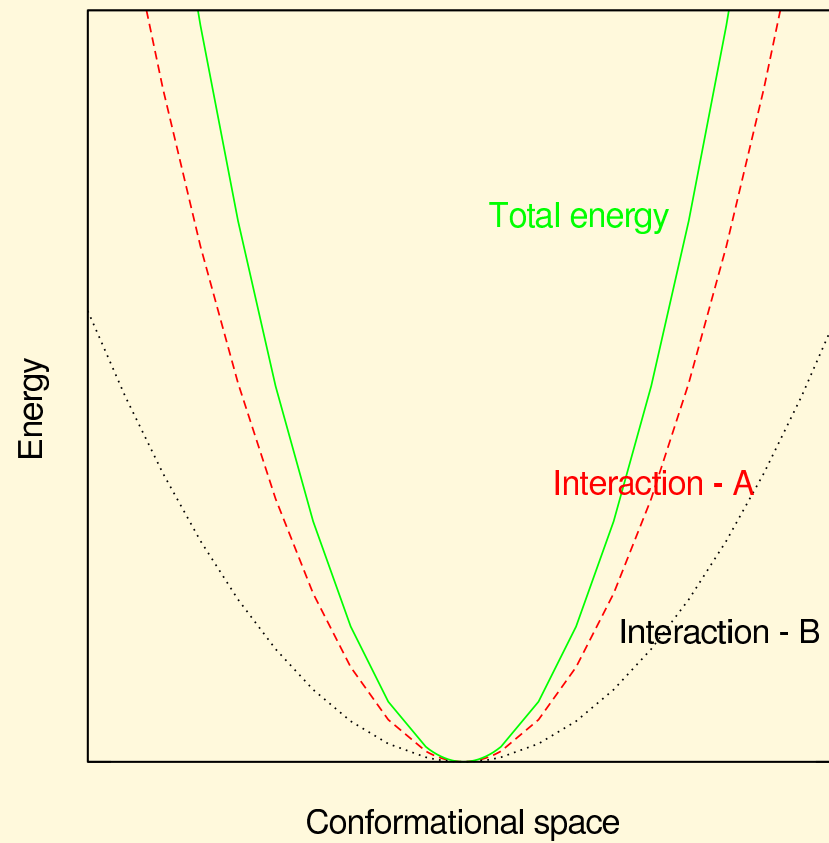
# Evidences which explicitly show such a consistency between interactions:

- **A consistency between intra- and inter-residue interactions:**

  - ⋆ The observed conformations of each residue in proteins mostly fall in the low-energy regions of the (ϕ, ψ) map of individual residues (Némethy & Scheraga, 1977)).

  - ⋆ Most side chains take conformations close to an energy minimum of isolated amino acid residues.

- **An overall consistency between backbone – side chain and side chain – side chain interactions:**

  - ⋆ Native side chain conformations could be well predicted by taking account of only backbone – side chain interactions if all backbone atoms are fixed in their native conformation (Eisenmenger et al., 1993),

  - ⋆ although the side chain – side chain interactions contribute to the stabilization of the native conformations of side chains (Tanimura et al., 1994).

A principle of minimal frustration in the energy landscape of natural proteins

Bryngelson & Wolynes (1987) pointed out that:

- A rough energy landscape, a frustrated situation which is caused by many competing interactions, is a characteristic of random copolymers and often causes glass transitions.

- The energy landscape for natural proteins must be minimally frustrated between smooth and rough energy landscapes and must resemble funnels for proteins to fold into single stable structures within a limited time.

Inconsistent/Frustrated Energy Landscape

Total energy

Energy

Interaction - B

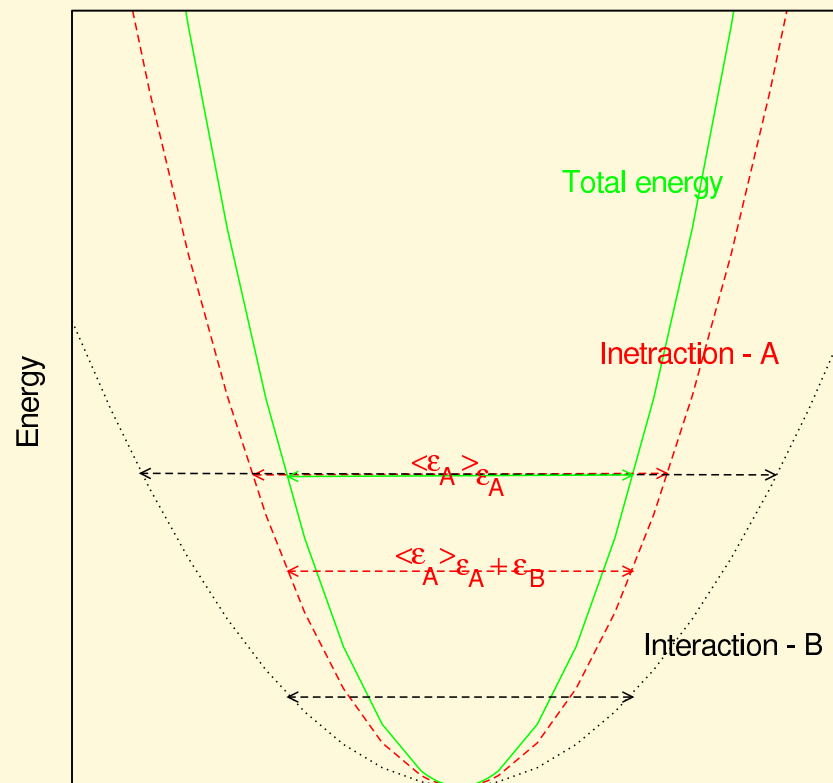Interaction - A

Conformational space
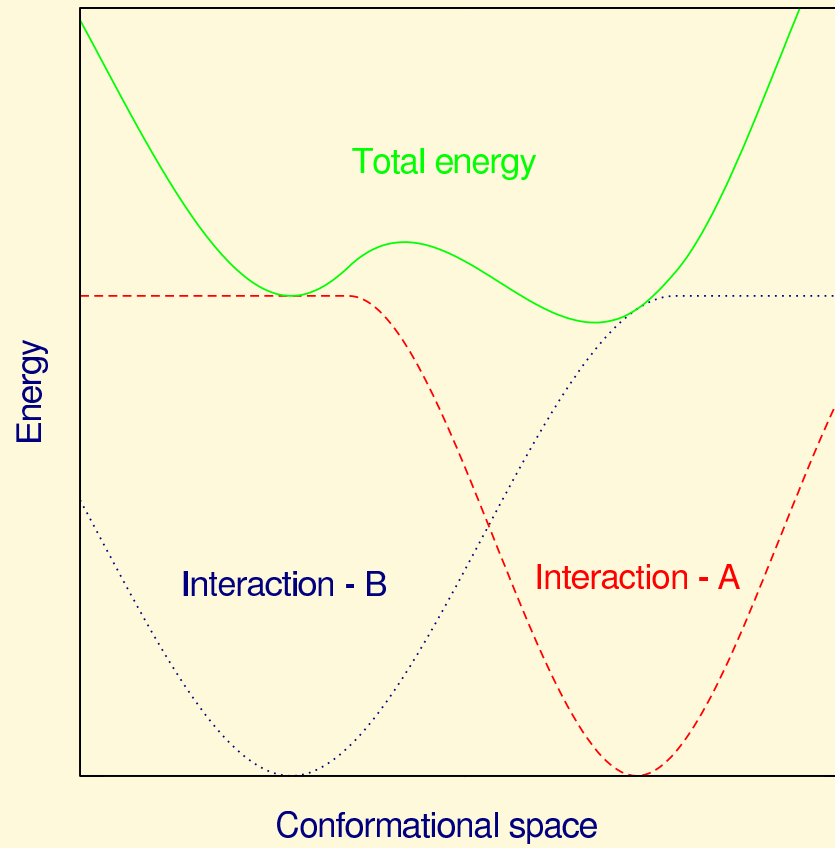
The consistency and minimal frustration among various interactions in protein native structures are essential for the stability and foldability of protein structures.

Here, we show short- and long-range interactions between residues in coarse-grained energy scales are consistent with each other for sequence selection of the more stable sequences for each protein.

- Interaction potentials used here are potentials of mean force evaluated from residue distributions observed in protein native structures:

  ★ the long-range contact potentials between the 20 kinds of amino acids (Miyazawa & Jernigan, 1985, 1996, 1999) and

  ★ the short-range secondary structure potentials based on peptide dihedral angles (Miyazawa & Jernigan, 1999).

- Sequence space is searched instead of conformational space by exchanging amino acids within each protein.

  ★ Evidence is provided that protein native sequences can be regarded approximately as samples from the statistical ensembles of sequences with these energy scales.
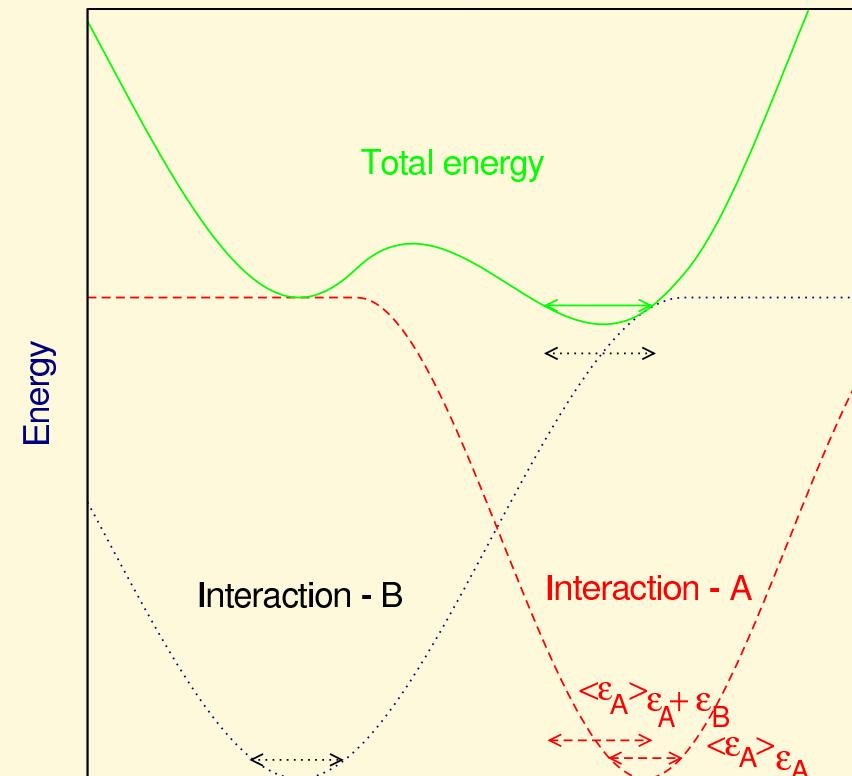
Consistencies between short- and long-range interactions are examined for their effects on the mean and the variance of interaction energies at statistical equilibrium in sequence space.

Consistent/Unfrustrated Energy Landscape

Inconsistent/Frustrated Energy Landscape

Total energy

Inetraction - A

$<\varepsilon_A>\varepsilon_A$

$<\varepsilon_A>\varepsilon_A+\varepsilon_B$

Interaction - B

Energy

Conformational / sequence space

Total energy

Energy

Interaction - B

Interaction - A

$<\varepsilon_A>\varepsilon_A+\varepsilon_B$

$<\varepsilon_A>\varepsilon_A$

Conformational / sequence space

2. METHODS

Stability of protein sequence and structure

An effective free energy, $\mathcal{F}$, which represents the stability of a sequence - structure pair, i.e., probability $P(s,i)$ of a specific conformation s for sequence i:

$$\beta\mathcal{F}(s|i) \equiv -\log(P(s|i)) \tag{1}$$

$$= \beta E^{conf}(s,i) + \log(\sum_s \exp(-\beta E^{conf}(s,i))) \tag{2}$$

where

$\beta \equiv 1/(kT),$

$E^{conf}(s,i)$ is the conformational energy of the conformational state s of sequence i.

$\sum_s$ is taken over all possible conformations.

The contribution from the partition function is approximated by assuming the condition under which native-like conformations are dominant:

$$\log(\sum_s \exp(-\beta E^{conf}(s, i)))$$

$$\simeq \log(\sum_{s \in \{\text{native-like}\}} \exp(-\beta E^{conf}(s, i)))$$

$$\simeq \log(\sum_{s \in \{\text{native-like}\}} 1) - \beta \sum_{s \in \{\text{native-like}\}} E^{conf}(s, i)/(\sum_{s \in \{\text{native-like}\}} 1)$$

$$\simeq n_r \sigma - \beta \langle E^{conf}(s, i) \rangle_{\beta=0}, \text{ native-like conf.}$$

$$(3)$$

where

n_r is the sequence length.

σ is a constant to represent the conformational entropy per residue in k units for native-like structures.

Thus, the effective free energy $\mathcal{F}(s,i)$ to represent the stability of conformation s and sequence i may be approximated as

$$\beta\mathcal{F}(s|i) \simeq \beta\mathcal{E}(s,i) + n_r\sigma \tag{4}$$

$$\beta\mathcal{E}(s,i) \equiv \beta E^{conf}(s,i) - \beta\langle E^{conf}(s,i)\rangle_{\beta=0}, \text{ native-like conf.} \tag{5}$$

where

$\mathcal{E}(s,i)$ is the conformational energy relative to the average over native-like conformations.

Coarse-grained conformational energy

- **Secondary structure energy:**

$$E^s(s, i) = \sum_p \delta e^s(s_{p-1}, i_p, s_p, s_{p+1}) \tag{6}$$

$$\langle E^s(s, i)\rangle_{\beta=0,\text{native-like conf.}} \simeq \sum_p \langle \delta e^s(s_{p-1}, i_p, s_p, s_{p+1})\rangle_{\text{all natives}} \tag{7}$$

where $\delta e^s(s_{p-1}, i_p, s_p, s_{p+1})$ is the interaction energy between the side chian of i_p type and the tripeptide of conformational state (s_{p-1}, s_p, s_{p+1}); p indicates a residue position. s_p is one of α, β, pro-β, L-α, L-β.

- **Pairwise contact energy:**

$$E^c(s, i) = \frac{1}{2} \sum_p \sum_j n^c_{i_p j}(e_{i_p j} - e_{rr}) \tag{8}$$

$$\langle E^c(s, i)\rangle_{\beta=0,\text{native-like conf.}} \simeq \frac{1}{2} \sum_p \langle n^c_{i_p j}\rangle_{\text{all natives}}(e_{i_p j} - e_{rr}) \tag{9}$$

where $e_{i_p j}$ is a contact energy between residues of i_p and j types, e_{rr} is a collapse energy independent of residue type, and $n^c_{i_p j}$ is the number of contacts between residues of i and j types at pth residue. **Here, we consider only sequences having the same amino acid composition as the native sequence.**

Statistical ensemble of sequences

The conditional probabilities $P(i|s)$ of sequences i for a given structure s :

$$P(i|s) = P(s|i)P(i)/\sum_i P(s|i)P(i) \tag{10}$$

$$P(i) = \text{constant} \tag{11}$$

where

$P(s|i)$ is the probability of a specific conformation s for sequence i.

$P(i)$ is the $a\ priori$ probability for sequence i.

$\sum_i$ means the sum over all sequences with fixed length for a given structure; here, we consider only sequences having the same amino acid composition as the native sequence.

Thus, $P(i|s)$ is represented as:

$$P(i|s) = \frac{1}{\mathcal{Z}}\exp(-\beta\mathcal{E}(s,i)) \tag{12}$$

$$\mathcal{Z} \equiv \sum_i \exp(-\beta\mathcal{E}(s,i)) \tag{13}$$

where

$\mathcal{Z}$ is a partition function for the ensemble of sequences

$\mathcal{E}(s,i)$ is the conformational energy relative to the average over native-like conformations.

Notations for statistical averages which are calculated in the present analyses:

$$\langle X \rangle_Y \equiv \frac{1}{\mathcal{Z}(Y)} \sum_i X(s,i) \exp(-\beta Y(s,i)) \tag{14}$$

$$\mathcal{Z}(Y) \equiv \sum_i \exp(-\beta Y(s,i))$$

For example,

$$\langle \mathcal{E}^c \rangle_{\mathcal{E}^s + \mathcal{E}^c} \equiv \frac{1}{\mathcal{Z}} \sum_i \mathcal{E}^c(s,i) \exp(-\beta(\mathcal{E}^s(s,i) + \mathcal{E}^c(s,i))) \tag{15}$$

$$\langle (\Delta\mathcal{E}^c)^2 \rangle_{\mathcal{E}^s + \mathcal{E}^c} \equiv \frac{1}{\mathcal{Z}} \sum_i (\Delta\mathcal{E}^c(s,i))^2 \exp(-\beta(\mathcal{E}^s(s,i) + \mathcal{E}^c(s,i))) \tag{16}$$

where

$$\Delta\mathcal{E} \equiv \mathcal{E} - \langle \mathcal{E} \rangle \tag{17}$$

Monte Carlo simulations to generate the statistical ensemble of sequences

- 100,000 residue exchanges per residue are tried in each protein with the Metropolis method.

- The conformational temperature $1/\beta$ is always taken to be one; so that the sum of the equilibrium distributions over all proteins are close to those observed in their native structures.

Datasets of protein structures used

- Proteins which belong to class 1 to 5 in Release 1.53 of the SCOP have been used.

- Only structures better than 2.5 Ådetermined by X-ray are used.

- Species representatives of 2129 proteins were used to estimate the statistical potentials.

- Family representatives of 797 proteins are used to analyze the statistical ensembles of sequences.
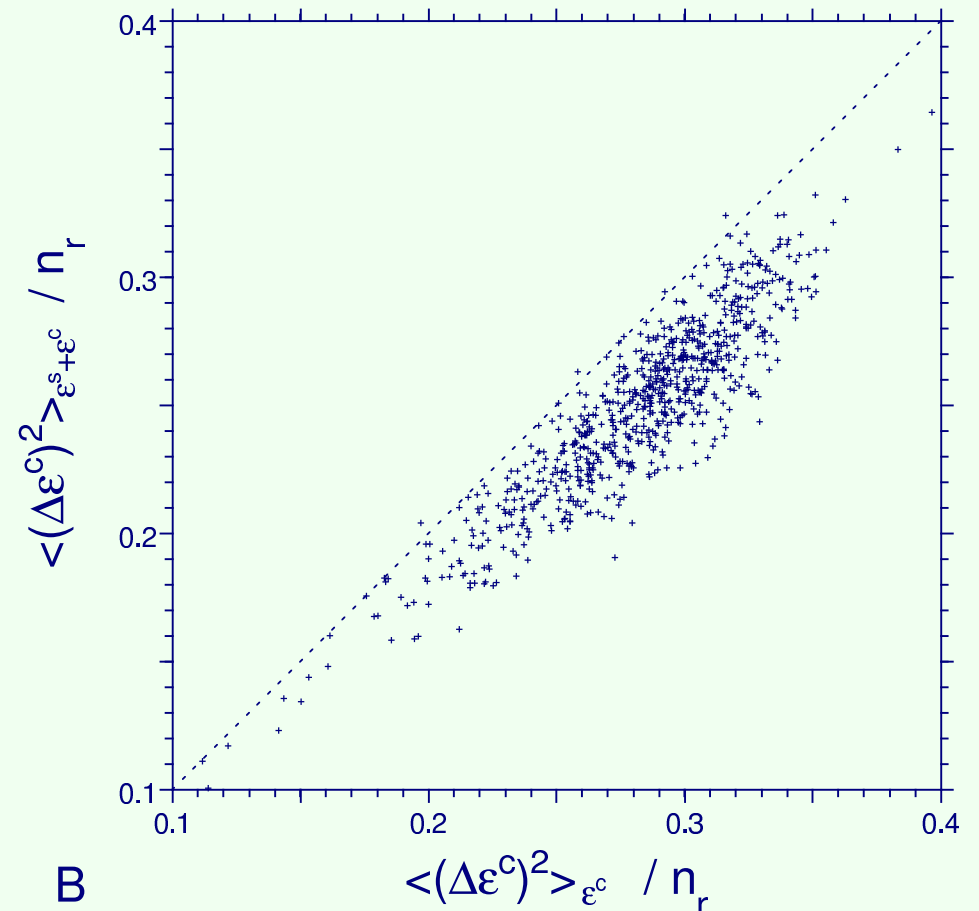
3. RESULTS

- $\langle \mathcal{E}^c \rangle_{\mathcal{E}^c} \ > \ \langle \mathcal{E}^c \rangle_{\mathcal{E}^s + \mathcal{E}^c}$

  for almost all proteins indicates that both classes of interactions are consistent with each other.
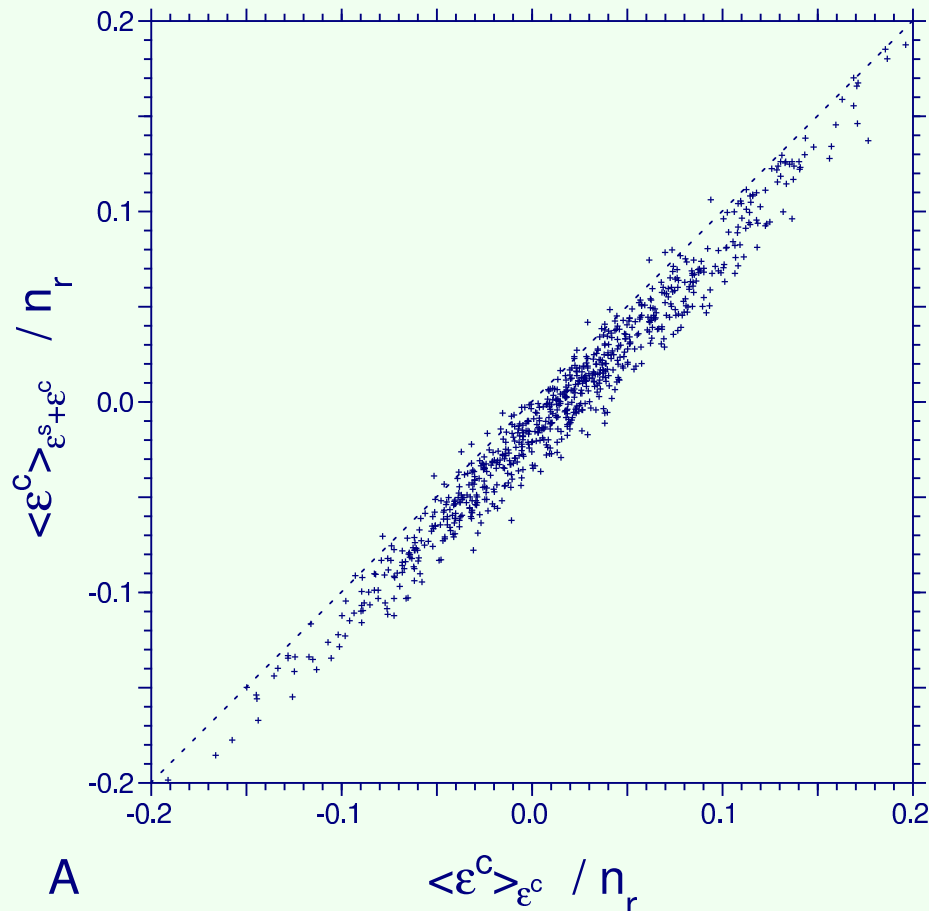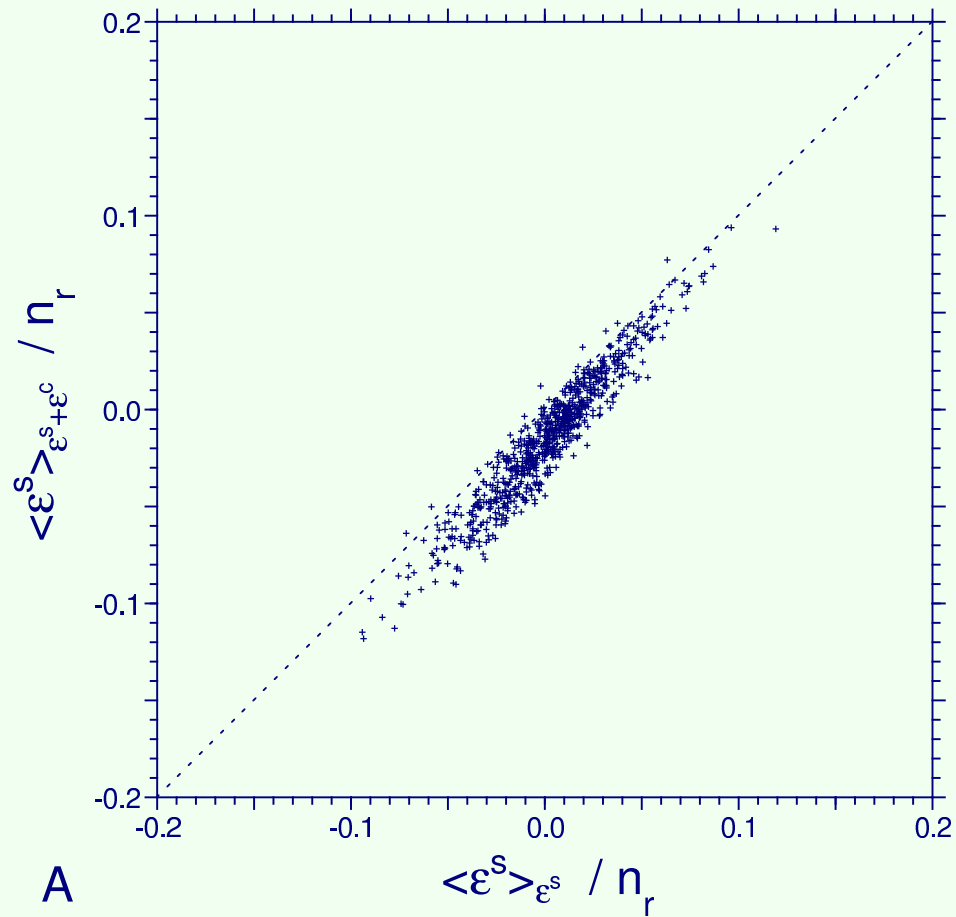
- $\langle (\Delta \mathcal{E}^c)^2 \rangle_{\mathcal{E}^c} \ > \ \langle (\Delta \mathcal{E}^c)^2 \rangle_{\mathcal{E}^s + \mathcal{E}^c}$
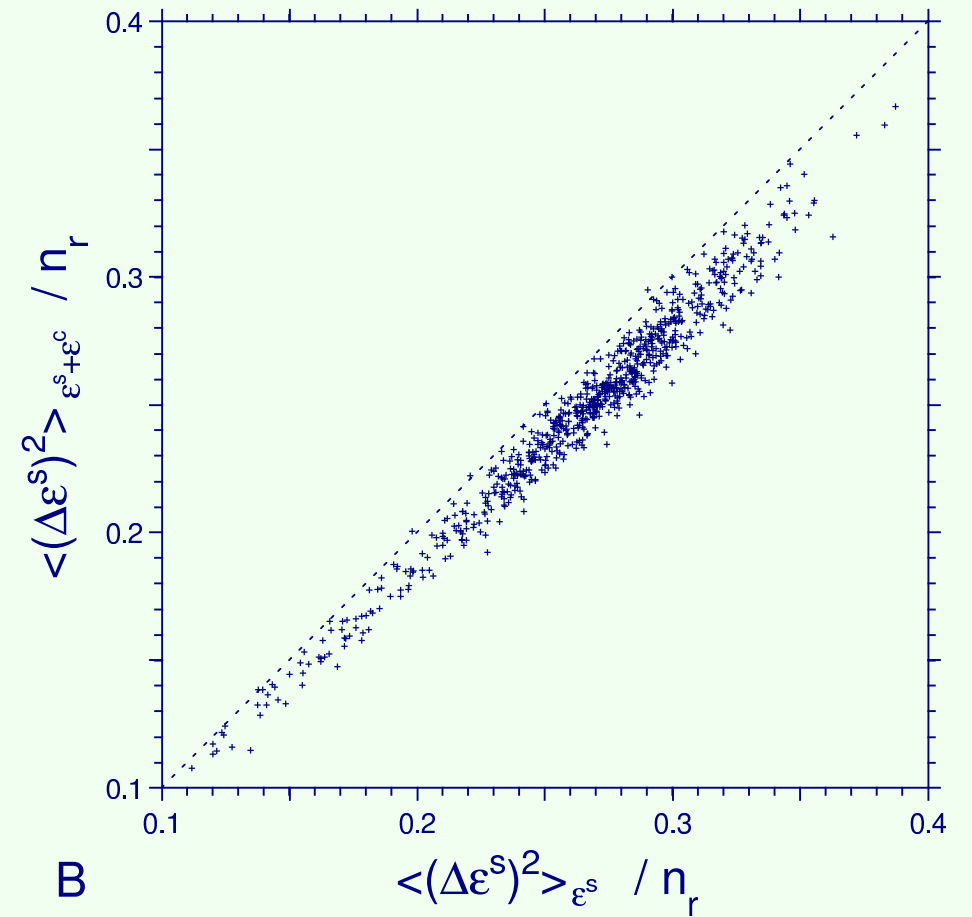
  for almost all proteins indicates that one class of interactions tend to reduce the available range of conformational space for the other class of interactions.
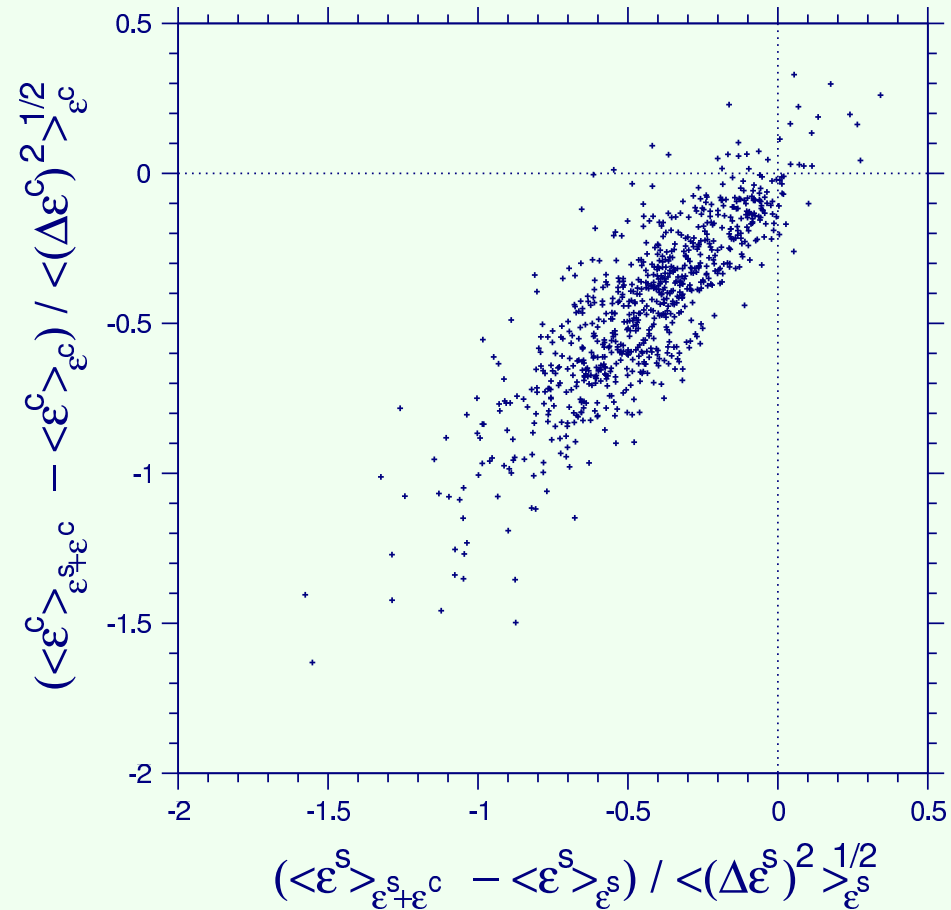

A

B

- $\langle \mathcal{E}^s \rangle_{\mathcal{E}^s} \;\; > \;\; \langle \mathcal{E}^s \rangle_{\mathcal{E}^s + \mathcal{E}^c}$

- $\langle (\Delta \mathcal{E}^s)^2 \rangle_{\mathcal{E}^s} \;\; > \;\; \langle (\Delta \mathcal{E}^s)^2 \rangle_{\mathcal{E}^s + \mathcal{E}^c}$

A

B

The decreases in the mean energies of one class by adding the other class of interactions range from 0 to -1 s.d. for both classes of interactions

Covariances between contact energies and secondary structure energies

Relation between the covariances and the increments of mean energies due to the change of interactions:

$$\int_0^1 \frac{\partial \langle \mathcal{E}^c \rangle_{x\mathcal{E}^s + \mathcal{E}^c}}{\partial x} \, dx \;=\; -\beta \int_0^1 \langle \Delta \mathcal{E}^s \Delta \mathcal{E}^c \rangle_{x\mathcal{E}^s + \mathcal{E}^c} dx \qquad (18)$$
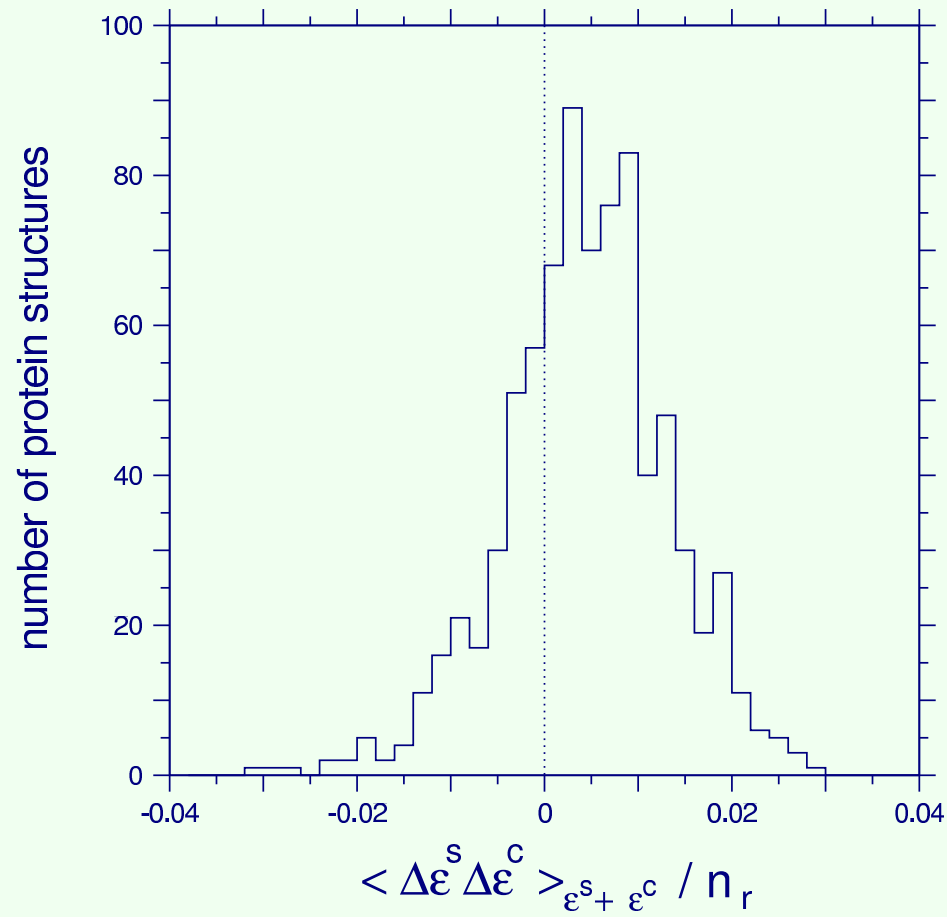
$$\int_0^1 \frac{\partial \langle \mathcal{E}^s \rangle_{\mathcal{E}^s + y\mathcal{E}^c}}{\partial y} \, dy \;=\; -\beta \int_0^1 \langle \Delta \mathcal{E}^s \Delta \mathcal{E}^c \rangle_{\mathcal{E}^s + y\mathcal{E}^c} dy \qquad (19)$$

- $\langle \Delta \mathcal{E}^s \Delta \mathcal{E}^c \rangle_{\mathcal{E}^s + \mathcal{E}^c} \;\sim\; 0$

  for almost all proteins.

- $\langle \Delta \mathcal{E}^s \Delta \mathcal{E}^c \rangle_{\mathcal{E}^s} \;>\; 0 \;\;,\; \langle \Delta \mathcal{E}^s \Delta \mathcal{E}^c \rangle_{\mathcal{E}^c} \;>\; 0$
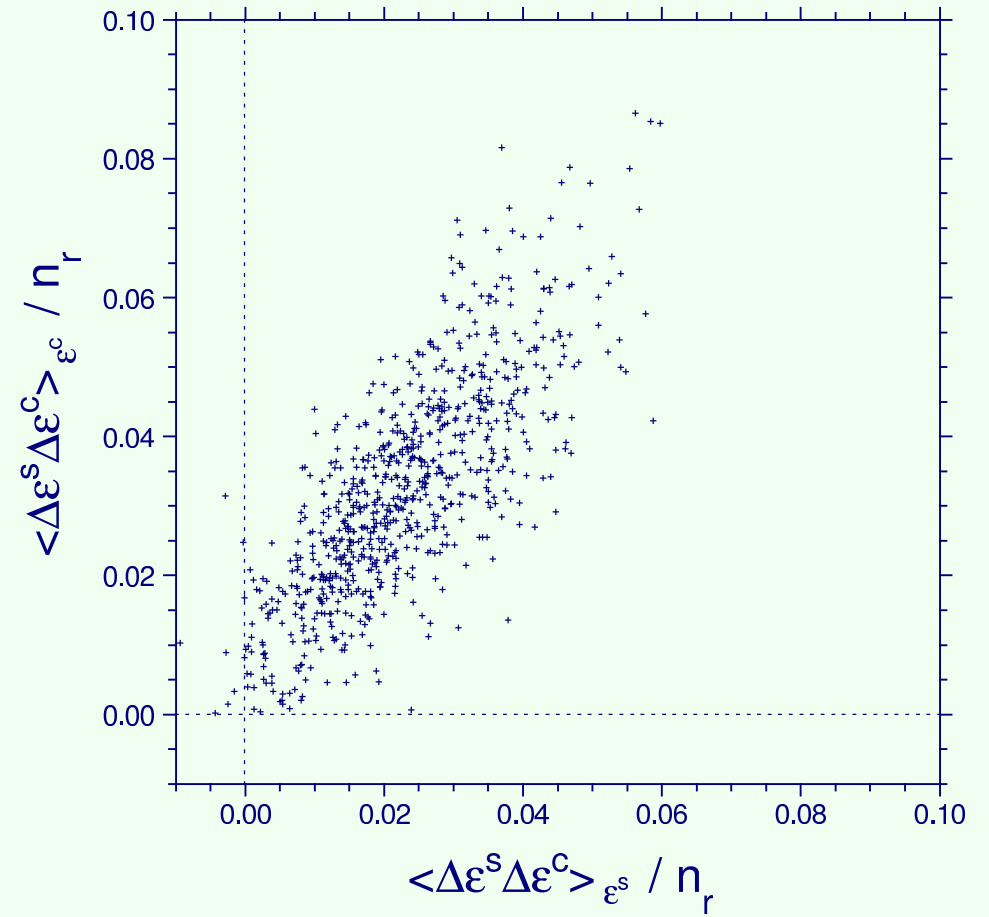
  for almost all proteins.

- $\langle \Delta \mathcal{E}^s \Delta \mathcal{E}^c \rangle_{\mathcal{E}^s + \mathcal{E}^c} \sim 0$

  for almost all proteins.

- $\langle \Delta \mathcal{E}^s \Delta \mathcal{E}^c \rangle_{\mathcal{E}^s} > 0$, $\langle \Delta \mathcal{E}^s \Delta \mathcal{E}^c \rangle_{\mathcal{E}^c} > 0$
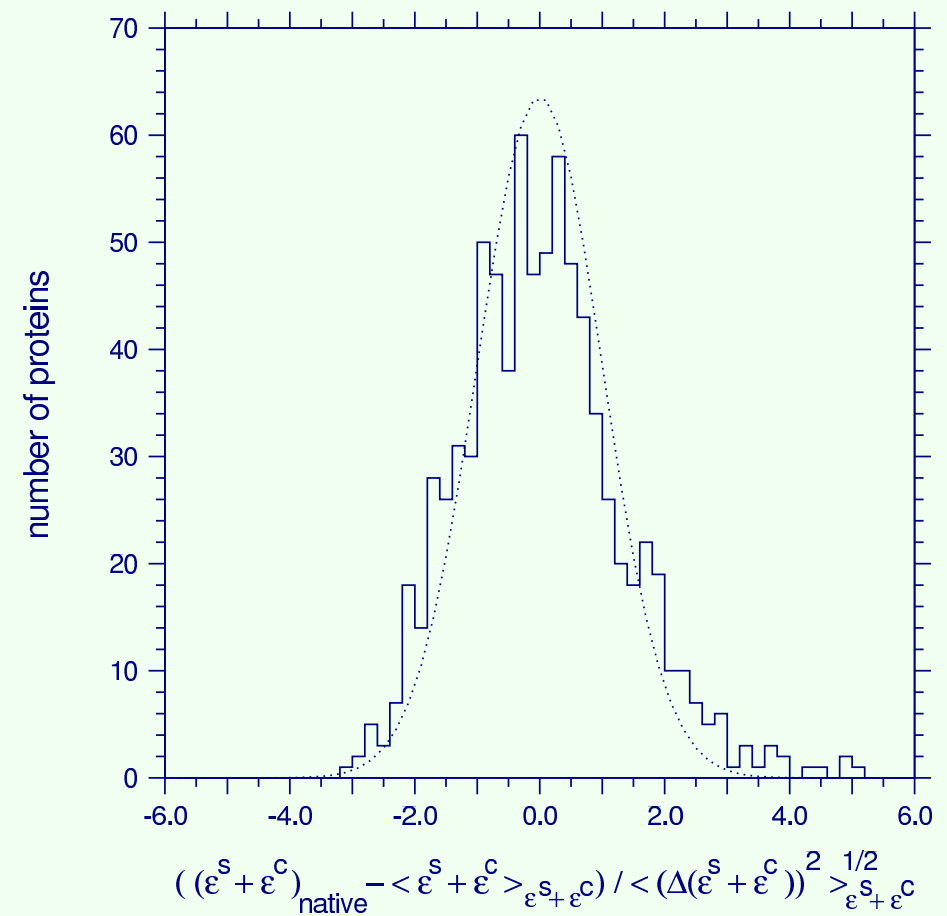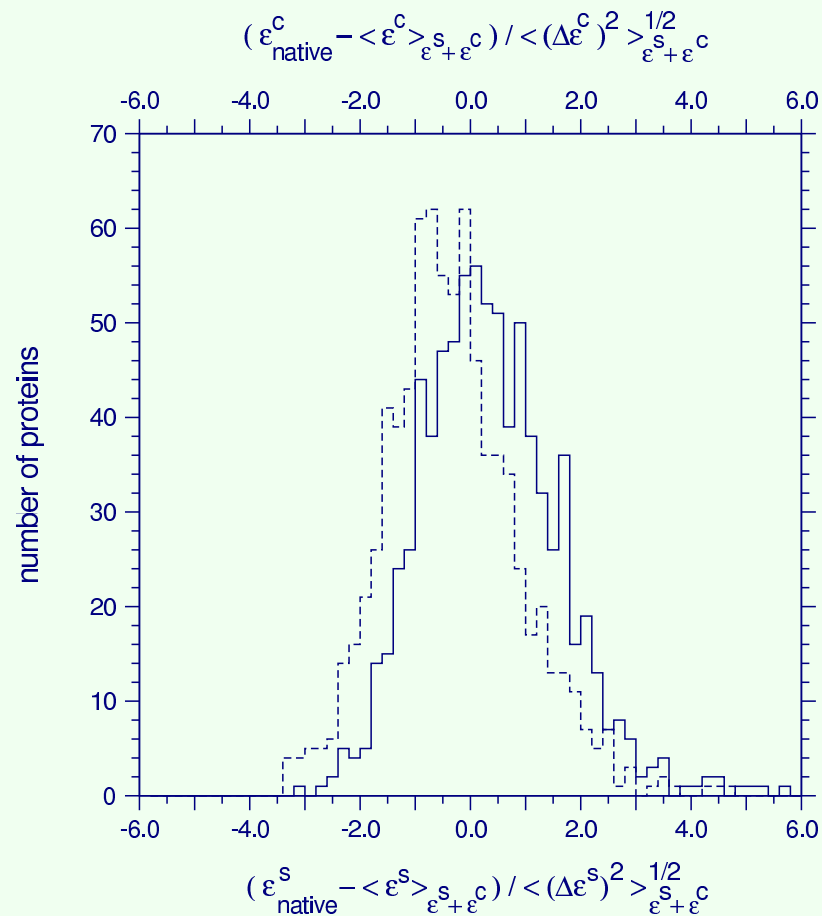
  for almost all proteins.

Can native protein sequences be regarded as samples at equilibrium in sequence space ?

- The total contact frequencies between the 20 kinds of amino acids observed in many protein native structures can be regarded with small relative errors ($\langle 10$ %) as contact frequencies at statistical equilibrium in sequence space (Miyazawa&Jernigan, 1999).

- Here it is shown that contact energies and secondary structure energies of most native proteins lie mostly within the statistical fluctuations around equilibrium in sequence space, and that there is no correlation between the deviations of both native energies from their statistical averages.

The frequency distribution for the total energies of native proteins is similar to a Gaussian distribution.

- For the contact and secondary structure energies
- For the total energies

$$(\varepsilon^c_{native} - <\varepsilon^c>_{\varepsilon^s + \varepsilon^c}) / <(\Delta\varepsilon^c)^2>^{1/2}_{\varepsilon^s + \varepsilon^c}$$

$$(\varepsilon^s_{native} - <\varepsilon^s>_{\varepsilon^s + \varepsilon^c}) / <(\Delta\varepsilon^s)^2>^{1/2}_{\varepsilon^s + \varepsilon^c}$$

$$((\varepsilon^s + \varepsilon^c)_{native} - <\varepsilon^s + \varepsilon^c>_{\varepsilon^s + \varepsilon^c}) / <(\Delta(\varepsilon^s + \varepsilon^c))^2>^{1/2}_{\varepsilon^s + \varepsilon^c}$$

number of proteins

There is clearly no correlation between the deviations of secondary structure and contact energies for each native protein from their statistical averages.

$\implies$ All proteins have the same conformational temperature.
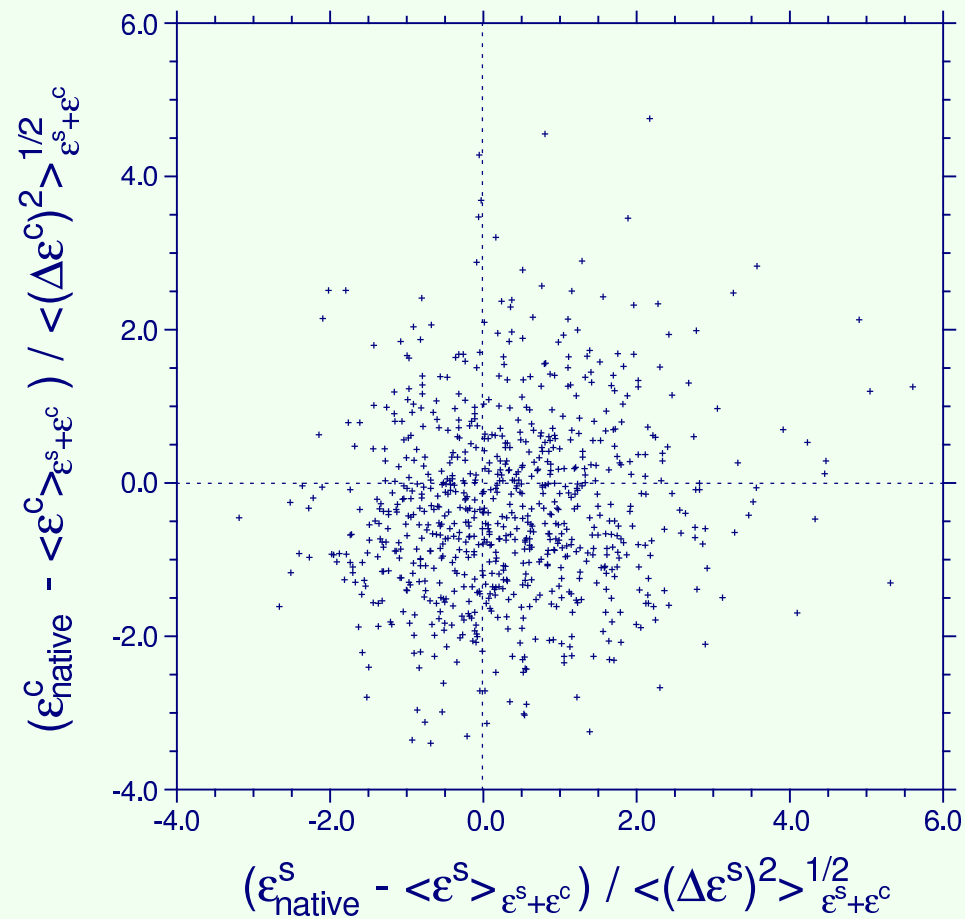
4. CONCLUSIONS

- **Short-range secondary structure interactions and long-range contact interactions in coarse-grained energy potentials are consistent/minimally-frustrated with each other for a statistical equilibrium with residue exchanges in protein sequences.**

  Proteins must have achieved these unique characteristics of smoothing the energy landscape on a coarse-grained conformational scale over the course of molecular evolution.

- **Protein native sequences can be regarded approximately as samples from equilibrium ensembles of sequences with these energy scales, and in addition all proteins have the same conformational temperature.**