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# Modeling the Free Energy of Polypeptides in Different Environments

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The free energy for increasing the content of helical and elongated backbone segments in polypeptides is estimated performing computer simulations of “reasonable” random walks for all-atom models of isolated single chains. A summary of the applications on several homo polypeptides ( $X_{40}$  with  $X=G,A,V,T,K,E$ ) and on the  $A\beta(1-40)$  peptide involved in Alzheimer disease is reported.

## 1 Introduction

The aggregation propensity, a consequence of the protein sequence and of its environment, can be the indirect effect of the absence of a folding propensity<sup>1,2</sup>. This effect has been called “inverse side chain effect”<sup>3</sup> or “natively disordered model”<sup>2</sup>: some sequences, when merged into a given environment, do not find a pathway to fold into protected structures and are therefore more suited to form  $\alpha$ -specific backbone interactions that can eventually drive protein oligomerization.

We propose a model for measuring the competition between the formation of protected structures and structures suited to aggregation<sup>4</sup>. The propensity for a single chain  $a$  to adopt a given value,  $x$ , for a global configurational variable,  $X(\mathbf{r})$  ( $\mathbf{r}$  being the configuration of all atoms in the molecule), is measured by the free energy  $f_a(x)$ . In the model, collective properties that monitor the secondary structure of peptides were used as  $x$ . Because of the relevance of helical and elongated segments in the structure of peptides involved in formation of fibrils, we focused on the construction of extended helical segments or, alternatively, of extended elongated segments in different sequences of 40 aminoacids.

## 2 Method

Random walks were performed by using the Monte Carlo method in the dihedral space of single chains, with moves associated to randomly chosen temperatures ( $T_{max} = 10000$  K), the PARM99 force-field, a short cut-off for nonbonding interactions (0.5 nm) and biasing potential linearly dependent on the collective chosen variable  $X$ . The helical content was

measured via the maximal number of consecutive residues with  $260^\circ < \phi < 320^\circ$  and  $297^\circ < \psi < 353^\circ$  ( $X = L_\alpha$ ). The  $\beta$ -strand content was measured as the maximal number of residues with  $150^\circ < \phi, \psi < 210^\circ$  ( $X = L_\beta$ , hereafter).

The free energy  $f_a(x) = u_a(x) - Ts_a(x)$  of chain  $a$  is given by the following equations. Assuming that the density of configurations is the average over all the biased metastatistics, the two contributions,  $s_a$  and  $u_a$ , to the free energy can be rewritten as:

$$\begin{aligned} s_a(x) &= R \log \left\{ \tilde{n}'_a(x) \right\} + R \log \left\{ (\exp(V))'_a(x) \right\} \\ u_a(x) &= u_{0,a} + d_a RT/2 + \frac{\int_v U_a(\mathbf{r}) \tilde{P}'_a(\mathbf{r}) \delta[X(\mathbf{r}) - x] d\mathbf{r}}{\tilde{n}'_a(x)} \end{aligned} \quad (1)$$

where:  $\tilde{n}'$  and  $\tilde{P}'$  are, respectively, the density of  $x$  and the configurational probability evaluated collecting the metastatistics of the bundle of biased random walks;  $V$  is the biasing potential (linear functions of  $x$ );  $v$  is the space spanned by configurations  $\mathbf{r}$ ;  $X(\mathbf{r})$  is  $L_\alpha$  or  $L_\beta$  (antagonist);  $f_a$  is the free energy in state  $x$  of chain  $a$ ;  $u_a$  is its total energy in state  $x$ ;  $K_a = d_a RT/2$  is the kinetic part (with  $d_a$  torsional d.o.f.);  $u_{0,a}$  is the reference state for energy ( $L_{\beta,max}$ ).

The  $U_a(\mathbf{r})$  term is given by the force-field, this time including long-range corrections, and adding mean-field corrections for the environment. To take into account water solvation, finite difference solutions of the Poisson-Boltzmann equation for the polypeptide in water, together with solvent accessible surface area contributions, were included in  $U_a$ .

### 3 Results

Homo polypeptides with sequences  $X_{40}$  ( $X=G,A,V,T,K,E$ ) were studied. Their helical and  $\beta$ -strand propensity was compared with the  $A\beta(1-40)$  peptide involved in the Alzheimer disease and several peptides with the  $A\beta$  sequence randomly scrambled.

As a summary of this study, here we report in Fig. 1 the comparison between the free energy of the chosen variables for  $G_{40}$ ,  $A_{40}$ ,  $V_{40}$  and  $A\beta(1-40)$ , in water solution (panel a) and in the vacuum (panel b), this latter modeling the membrane environment. The  $f$  profiles are shifted for graphical purposes.

Gly is unstructured in water solution, displaying only a moderate resistance towards extending its  $\beta$ -strand content. In a membrane-like environment, this resistance is almost completely lost and even small intermolecular interactions can easily stabilize extended  $\beta$ -sheets. Ala displays an opposite behavior: both in water solution and in the membrane-like environment the chain displays a high propensity of being structured in helical segments, while the resistance to extend  $\beta$ -strand content is large. Val displays an intermediate behavior: in water, the propensity for extending helical segments is similar to that of Gly, but the resistance to extend  $\beta$ -strands is similar to that of Ala; in the vacuum, the propensity for extending helical segments is similar to Ala. The  $A\beta(1-40)$  peptide displays a behavior that is similar to Val homo polypeptide. The significant propensity of extending helical segments in the membrane-like environment is expected, being  $A\beta(1-40)$  part of the membrane protein APP. But this propensity is almost entirely lost in water solution, where the  $f(L_\alpha)$  profile is almost flat. On the other hand, no significant decrease in the resistance

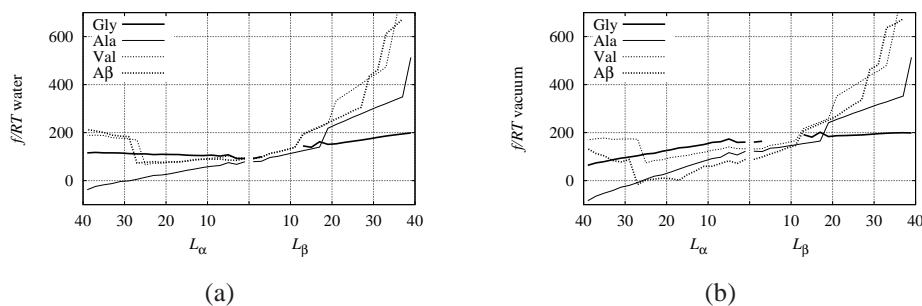


Figure 1. Comparison between free energy  $f(L_\alpha)$  (left  $x$ -axis) and  $f(L_\beta)$  (right  $x$ -axis) in Eq. 1 between several peptides, in water solution (a) and in the vacuum (b).

of extending  $\beta$ -strand is displayed when the peptide is extracted from the membrane-like environment into the water solution.

The similarity between A $\beta$ (1-40) and Val<sub>40</sub>, together with comparisons with other helical or  $\beta$ -strand propense peptides (data not shown here), implies that no significant propensity for extending  $\beta$ -strand length is encoded in the A $\beta$ (1-40) sequence. Rather, a significant loss of propensity for extending helical content is displayed when the peptide is moved from the membrane to the water solution: aggregation is more the result of a low propensity for intramolecular folding than for a specific propensity for extending  $\beta$ -strands.

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