Analysis of Amphiphilic Periodicity of α-Helices : Detection of Edges of Helices and Functional Residues in Proteins

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Abstract

Amphiphilic periodicity of protein segments is often used as a profile for secondary structure prediction of helices. Helical amphiphilicity of soluble proteins are often disrupted by several hydrophilic residues located in the hydrophobic core. Although these residues can be a negative factor for the structural stability of soluble proteins, they probably contribute to a specific function, for example, yielding polar interactions to pack the whole chain into a compact and stable conformation. We have developed a program to detect such amphiphilicity disrupting residues from the amino acid sequence. Analysis of known protein structures indicates that these residues can be related to functions, packing of soluble proteins, or edges of helices of soluble and membrane proteins.

1 Introduction

Rapid DNA sequencing methods are providing amino acid sequences of numerous proteins. In order to understand three-dimensional protein structures and their functions, computational prediction systems need be developed. Secondary structures, especially α-helices, often appear in many proteins. On a helix, there must be residues related to protein functions or interactions between the helix and other segments, but the existing secondary structure prediction methods do not provide such information.

Our program can detect hydrophilic residues located on a hydrophobic side of an amphiphilic helix by calculation of helical periodicity profiles with, what we call, computational point mutation (CPM). This is done by changing hydrophilic residues into alanine residues and if the amphiphilicity improves the original residues are candidates of irregular residues disrupting amphiphilic helices. Existence of these irregular residues can be interpreted from two viewpoints, structural stability and function. The former is that irregulars are likely to appear at the ends of helices or associated with polar interaction for packing of helices and other segments. The latter is that irregulars within the α-helices are expected to play important roles for specific functions of proteins, for example, attaching heme to hemoglobin or myoglobin.

We present the algorithm and discuss where and why irregular residues appear.

2 Methods

CPM method is the following: 1. Each residue within a certain span of given sequence is assigned a numerical hydrophobic index value [1]. 2. Two hydrophilic residues are selected within the span and changed into alanine. 3. Among all possible combinations of mutating hydrophilic residues, the highest value of the periodicity profile μ [2] is compared with that of the original sequence. 4. If μ

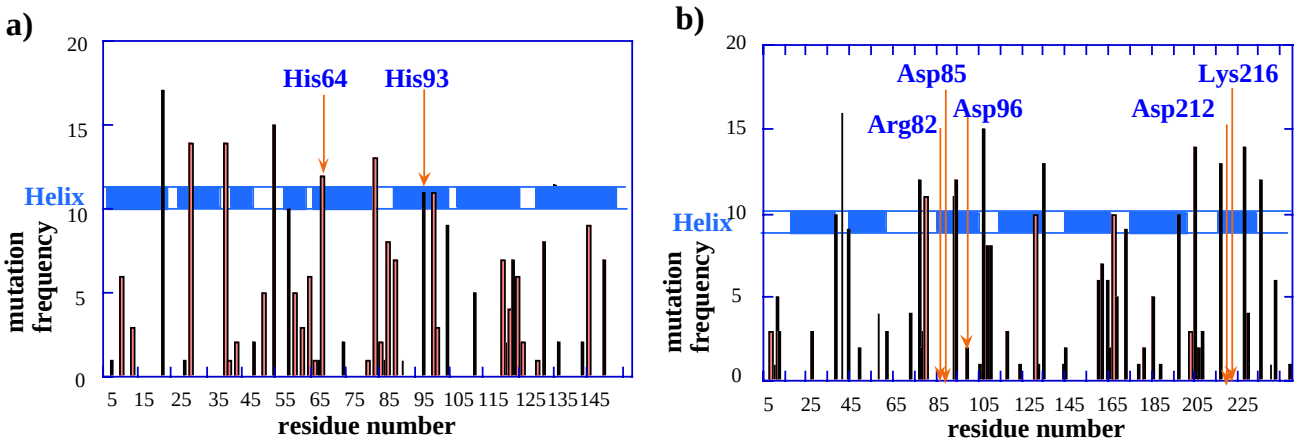

Figure 1: Histograms of CPM frequency a) myoglobin (1YMB) b) bacteriorhodopsin (2BRD) Shaded boxes represent known helix regions.

is higher for the mutant segment, a mutation count is given to each of the two mutated residues. 5. This procedure is repeated for the entire sequence.

In step 2, we replaced two hydrophilic residues at a time, since double mutation of irregular residues located on the same surface on a helix would give a higher profile than single mutation. This program displays the result as a histogram of the mutation frequency against the residue number i. In the histogram, highly mutated residues are regarded as irregular residues for helices.

3 Results and Discussion

We examined globins such as hemoglobin and myoglobin and compared location of irregular residues with known helix regions. Furthermore, we also examined membrane proteins such as bacteriorhodopsin. In both cases, irregular residues were concentrated at the ends of helices. However functional residues such as heme-binding histidine residues of the globins were also irregular residues even though they existed not at the ends but within helix regions (Figure 1(a)). According to the histogram of bacteriorhodopsin (Figure 1(b)), important residues for the function of proton pump (R82, D85, D96, D212 and K216) did not seem to be irregular residues.

To combine our method with existing profiles such as a hydropathy plot and a normal periodicity analysis, it will be possible to offer more accurate secondary structure prediction and function prediction.

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