Predicting Residue-wise Contact Orders of Native Protein Structure from Amino Acid Sequence

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Abstract

Residue-wise contact order (RWCO) is a new kind of one-dimensional protein structures which represents the extent of long-range contacts. We have recently shown that a set of three types of one-dimensional structures (secondary structure, contact number, and RWCO) contains sufficient information for reconstructing the three-dimensional structure of proteins. Currently, there exist prediction methods for secondary structure and contact number from amino acid sequence, but none exists for RWCO. Also, the properties of amino acids that affect RWCO is not clearly understood. Here, we present a linear regression-based method to predict RWCO from amino acid sequence, and analyze the regression parameters to identify the properties that correlates with the RWCO. The present method achieves the significant correlation of 0.59 between the native and predicted RWCOs on average. An unusual feature of the RWCO prediction is the remarkably large optimal half window size of 26 residues. The regression parameters for the central and near-central residues of the local sequence segment highly correlate with those of the contact number prediction, and hence with hydrophobicity.

*Key words:* protein structure prediction, residue-wise contact order, one-dimensional structure, linear regression.
Introduction

One of the main goals of protein structure prediction is to provide an intuitive picture of the relationship between the amino acid sequence and the native three-dimensional (3D) structure of proteins. To this end, a number of methods have been developed for ab initio or de novo protein structure prediction. However, such methods are usually very complicated and make it difficult to intuitively understand the relationship between amino acid sequence and 3D structure. In this respect, one-dimensional (1D) structures of proteins may be conventional intermediate representations of both sequence and structure of proteins as it is easy to grasp the correspondence between sequence and structural characteristics.

Since 1D structures are 3D structural features projected onto strings of residue-wise structural assignment, a large part of 3D information appears to be lost. That is, the correspondence between amino acid sequence and 1D structures does not seem to be sufficient for uncovering the correspondence between amino acid sequence and 3D structure. However, Porto et al. have recently shown that the contact matrix of a protein structure can be uniquely recovered from its principal eigenvector. Since the protein 3D structure can be recovered from the contact matrix, the result of Porto et al. indicates that the information contained in the 3D structure can be expressed as a one-dimensional representation. Furthermore, we have recently shown that 3D structure of proteins can be reconstructed from a set of three types of 1D structures. In other words, the 3D structure of a protein is essentially equivalent to a set of three types of 1D structures. These 1D structures are namely secondary structure, contact number and residue-wise contact order. The fact that the 3D structure of a protein can be recovered from a set of these 1D structures opens a new possibility for elucidating the sequence-structure relationship of proteins.

The secondary structure of a protein is a string of symbols representing α helix, β strand, or coils. The contact number of each residue in a protein is defined
by the number of contacts the residue makes with other residues in the protein. More precisely, if we represent the contact map of the protein by $C_{i,j}$ ($C_{i,j} = 1$ if the $i$-th and $j$-th residues are in contact, or $C_{i,j} = 0$ otherwise), the contact number $n_i$ of the $i$-th residue is defined by $n_i = \sum_j C_{i,j}$. Similarly, the residue-wise contact order (RWCO) $o_i$ of the $i$-th residue of a protein is defined by $o_i = \sum_j |i - j|C_{i,j}$, that is, a sum of sequence separations between the residue and the contacting residues. The contact order was first introduced as a per-protein quantity by Plaxco et al. to study the correlation between protein topology and folding rate. The RWCO introduced here is a generalization of the contact order, and is a per-residue quantity.

At least in principle, if we can predict those 1D structures, we can also construct the corresponding 3D structures. Many accurate methods have been developed for secondary structure prediction. We have developed a method to predict the contact number from amino acid sequence with the average correlation of 0.63 between the native and predicted contact numbers. However, there is no method for predicting RWCO from amino acid sequence to date, and it is not clear if the prediction is possible at all. The primary objective of the present paper is to develop a method to predict RWCO from amino acid sequence.

While the accurate prediction of structural properties is important for its own sake, for a thorough understanding of the sequence-structure relationship, we still need to identify the properties of amino acid sequence that determine the structure. From the vast amount of studies on secondary structure prediction in the past, we are now convinced that each amino acid has a particular propensity for a particular secondary structure, although the final secondary structures in the native structure are determined in the global context. Also, contact number is closely related to the hydrophobicity of amino acids. Thus, both secondary structure and contact number have clear connections with the properties of amino acids. As for the residue-wise contact order, its geometrical meaning is clear (i.e., a quantity related
to the extent of long-range contacts), but the conjugate properties of amino acids are not. As the second objective of the present study, we attempt to identify the amino acids’ property affecting RWCO by examining the parameters derived for the prediction method.

The prediction method developed in this paper is based on a simple linear regression scheme which was also applied to the contact number prediction in our previous study. By examining the regression parameters, we show that the RWCO is primarily determined by the pattern of hydrophobicity of amino acids. Although the method is extremely simple, it yields a significant correlation of 0.59 between the native and predicted RWCOs. While further refinement is definitely necessary to apply the method for 3D structure prediction, the present method will serve as a basis for more elaborate methods yet to be developed.

**Materials and Method**

**Definition of residue-wise contact order**

As mentioned in the Introduction, the residue-wise contact order (RWCO) of the $i$-th residue is defined by

$$o_i = \frac{1}{L} \sum_{j:|j-i|>2} |i-j|C_{i,j}$$

(1)

where the summation is normalized by the length $L$ of the amino acid sequence of the protein and $C_{i,j}$ represents the contact map of the protein. We exclude trivial contacts between nearest- and next-nearest residues along the sequence. To make the RWCO useful for molecular dynamics simulations, the contact between two residues is defined by a smooth sigmoid function:

$$C_{i,j} = 1 / \{1 + \exp[w(r_{i,j} - d_c)]\}$$

(2)

where $r_{i,j}$ is the distance between $C_\beta$ atoms of the $i$-th and $j$-th residues ($C_\alpha$ atoms for glycine), $d_c$ is the cut-off distance for the contact definition, and $w$ is a
parameter that determines the sharpness of the sigmoid function. To be consistent with our previous studies\cite{6, 4}, we set $d_c = 12\AA$ and $w = 3$ throughout the present paper.

We also define the normalized (relative) RWCO by

$$y_i^p = \frac{(o_i^p - \langle o_i^p \rangle)}{\sqrt{\langle (o_i^p - \langle o_i^p \rangle)^2 \rangle}}$$

(3)

where $\langle \cdot \rangle$ denotes averaging operation over the given protein chain $p$.

**Prediction scheme**

To predict the RWCO of each residue in a protein, we first conduct three iterations of PSI-BLAST\cite{7} search against the NCBI non-redundant amino acid sequence database to obtain the sequence profile of the protein with the E-value cut-off of $10^{-7}$. We use the amino acid score table of the PSI-BLAST profile which is represented as $f(i, a)$ ($i$: site, $a$: amino acid) in the following (instead of the frequency table used in the previous study\cite{6}).

The RWCO $\tilde{o}_i^p$ of the $i$-th residue in the protein $p$ is predicted in two steps. First we predict the normalized RWCO $y_i^p$ for each residue, and then we combine it with the mean $\mu^p$ and standard deviation (S.D.) $\sigma^p$ of the RWCOs of the protein, which are predicted separately. The normalized RWCO is predicted by the following linear regression scheme:

$$\hat{y}_i^p = \sum_{m=-M}^{M} \sum_{a} C_{m,a} f^p(i + m, a) + C$$

(4)

where $M$ is the half window size (a free parameter to be determined), $f^p(i + m, a)$ represents an element of the PSI-BLAST profile of the protein $p$, and $C_{m,a}$ and $C$ are regression parameters. Both amino and carboxyl termini are treated by introducing an extra symbol for the “terminal residue.” Thus, the RWCO of the $i$-th residue is expressed as a linear function of the local sequence of $2M + 1$ residues surrounding the $i$-th residue.
The values of $C_{m,a}$ and $C$ are determined so as to minimize the prediction error over a database of protein structures. The error function is defined by

$$E = \sum_p \sum_i (y_{pi}^p - \hat{y}_{pi}^p)^2$$

(5)

where $y_{pi}^p$ is the observed normalized RWCO of the $i$-th residue of the protein $p$. The minimization of $E$ can be achieved by the usual least squares method.

The mean ($\mu^p$) and standard deviation ($\sigma^p$) of the RWCOs of a protein are predicted from the amino acid composition ($f_a^p$) and sequence length ($L^p$) of the protein $p$ in the same manner as we have done for the contact number prediction\[6\]. That is, the mean and S.D. are predicted by the following linear regression scheme:

$$\hat{\mu}^p = \sum_a A_a f_a^p + A F(L^p) + A$$

(6)

$$\hat{\sigma}^p = \sum_a D_a f_a^p + D F(L^p) + D$$

(7)

where $F(L^p) = L^p$ for $L^p < 300$ and $F(L^p) = 300$ for $L^p \geq 300$, and $A_a, A, D_a, D$ are regression parameters. The final value for the predicted absolute RWCO ($\hat{o}_{pi}^p$) is given by

$$\hat{o}_{pi}^p = \hat{\mu}^p + \hat{\sigma}^p \hat{y}_{pi}^p.$$  

(8)

**Data set**

We first selected representative proteins from each superfamily of all-$\alpha$, all-$\beta$, $\alpha/\beta$, $\alpha + \beta$, and multi-domain classes of the SCOP\[8\] (version 1.65) protein structure classification database through the ASTRAL\[9\] database. Those structures which were present in this superfamily representative set but were absent from the 40% representative set of ASTRAL, those containing chain breaks (except for termini), or those with the average contact number of less than 7.5 (non-compact structures) were discarded. Non-standard amino acid residues were converted to the corresponding standard residues when possible, otherwise discarded. When $C_\beta$ atoms were absent in non-glycine residues, they were modeled by the
SCWRL side-chain prediction program. After all, there remained 680 protein chains. The list of this data set will be available from the author’s website.

For training the parameters and testing the prediction accuracy, we performed a 15-fold cross-validation test. The 680 proteins were randomly divided into two groups, one consisting of 630 proteins for training the parameters (training set), and the other (test set) consisting of 50 proteins for testing the prediction using the parameters obtained from the training set. The procedure was iterated for 15 times.

**Measures of prediction accuracy**

We employ two measures for evaluating the prediction accuracy. The first one is the correlation coefficient ($\text{Cor}_p$) between the observed and predicted RWCOs for a given protein $p$, which is defined by

$$\text{Cor}_p = \frac{\langle (o_{i}^p - \langle o_i^p \rangle)(\hat{o}_{i}^p - \langle \hat{o}_i^p \rangle) \rangle}{\sqrt{\langle (o_i^p - \langle o_i^p \rangle)^2 \rangle} \sqrt{\langle (\hat{o}_i^p - \langle \hat{o}_i^p \rangle)^2 \rangle}}.$$  \hspace{1cm} (9)

The $\text{Cor}_p$ measures the consistency of the normalized RWCOs. In order to measure the accuracy of the predicted absolute values, we use the RMS error divided by the standard deviation of the observed RWCO ($\text{Dev}_A_p$):

$$\text{Dev}_A_p = \frac{\sqrt{\langle (o_i^p - \hat{o}_i^p)^2 \rangle}}{\sqrt{\langle (o_i^p - \langle o_i^p \rangle)^2 \rangle}}.$$  \hspace{1cm} (10)

**Results**

**Optimal window size**

In the prediction scheme presented in this paper, the half window size $M$ is a free parameter. We determine its value so that the prediction accuracy is maximized. We have performed a 15-fold cross-validation test with $M$ ranging from 0 to 40. The result is summarized in Figure II. The correlation coefficient $\text{Cor}_p$ (averaged
over the test sets) ranges from 0.48 at $M = 0$ to $\approx 0.59$ at $M = 26$ (Figure 1A). It should be noted that the correlation of 0.48 is already statistically significant given the average sequence length (172 residues) of the proteins in the data set.

The value of $Cor_p$ monotonically increases from $M = 0$ to $M = 26$, but starts to saturate for $M > 20$ and decreases slowly for $M > 26$. The deviation $DevA_p$ (averaged over the test sets) shows a consistent trend with $Cor_p$ (Figure 1B), and it reaches the minimum value of $\approx 1.03$ at $M = 26$. Thus, the optimal window size has been determined to be $M = 26$.

This optimal window size of $M = 26$ is much larger than the ones for any other 1D structure predictions. As far as we are aware, this is the longest range of correlation observed between 1D structure and amino acid sequence. For example, the optimal half window size is $M = 9$ for contact number prediction (see below) and $M = 6 - 8$ for secondary structure prediction. Large window sizes usually result in over-fitting the training data, but such is not the case for RWCO prediction, as we have performed cross-validation tests. This unusually long-range correlation with amino acid sequence is a conspicuous property of the RWCO.

**Distribution of correlation**

As indicated by the average values of $Cor_p$ and $DevA_p$, the linear regression method with $M = 26$ tends to produce more accurate predictions than with other window sizes. However, the prediction accuracies for individual proteins do differ significantly as shown in Figure 2. While most of the proteins are decently predicted with correlations of 0.5 or higher, some proteins exhibit very poor correlations. The poorly predicted proteins are found not well-packed due to the small size of the protein (e.g., SCOP domain d1fs1a1), a large fraction of structurally disordered regions (e.g., d1cpo_1), or being a subunit of a large complex (e.g., d1mtyg_).
The prediction accuracy does not strikingly differ depending on the structural class of proteins (Table 1). However, all-α proteins show slightly poorer correlations compared to other classes, and α + β proteins show relatively better correlations. The latter may be due to the over-dominance of the α + β proteins in the data sets.

In Figure 3, three examples of predicted RWCO are shown. Despite the relatively good correlation between the native and predicted RWCOs, the absolute values of predicted RWCOs at many sites significantly differ from the corresponding native RWCOs. This behavior is indicated by the relatively large value of DevA_p ≈ 1.03 (Figure 1B). In particular, we notice that RWCOs of large values are consistently underestimated. This behavior suggests that some cooperative effects be taken into account for better prediction. Provided that the present method is based exclusively on one-body terms (Eq. 4), the prediction accuracy achieved is satisfactory, at least qualitatively.

**Regression parameters as functions of sequence position**

Since the present study is the first attempt to develop a prediction method for RWCO, it is of interest to examine the properties of amino acid residues that affect the RWCO, which are reflected in the values of the regression coefficients C_m,a. Figure 4 shows the values of C_m,a for each amino acid type a as a function of the window position m. For all the amino acid types, the peak of C_m,a, when present, is at the center (m = 0). We can easily recognize that these values, those at m = 0 in particular, are related to the hydrophobicity of amino acids. That is, C_0,a > 0 for hydrophobic residues and C_0,a < 0 for hydrophilic residues. When the amino acid index (AAindex) database was scanned for indices that highly correlates with C_0,a, we have found various hydrophobicity scales with correlations with C_0,a over 0.90 (data not shown). Therefore, we can conclude that the RWCO is primarily determined by the pattern of hydrophobicity along the sequence.
Some amino acid types exhibit oscillation with the periodicity of 3 to 4 residues, which is expected for the $\alpha$ helix. In fact, such residues (e.g., GLU, GLN, ALA, etc.) are of high $\alpha$ helix propensity. On the contrary, the residues of high $\beta$ strand propensity (e.g., ILE, VAL, etc.) do not exhibit such oscillation. Therefore, in addition to the hydrophobic properties, the parameters for RWCO also contain information for secondary structures.

**Discussion**

**Comparison with contact number prediction**

As can be seen from their definitions, the native RWCOs and contact numbers show a high correlation of 0.7 (data not shown). This is also consistent with the finding that RWCOs are primarily determined by hydrophobicity. Because of the correlation between RWCO and contact number, it is of interest to ask whether it is possible to “predict” RWCOs using contact number prediction, and vice versa. The result of this “cross-prediction” is listed in Table 2. Here, the contact number prediction is based on exactly the same linear regression scheme as the RWCO prediction method. In order to make consistent the quality of the two different prediction methods, we have determined the regression parameters and the optimal half window size for the contact number prediction using the same training and test data sets as used here. The resulting contact number prediction method yields the average prediction accuracy of $Cor_p \approx 0.70$ and $DevA_p \approx 0.803$ with the optimal half window size of 9 (Table 2, Case B), a remarkable improvement over our previous study ($Cor_p \approx 0.63$ and $DevA_p \approx 0.941$) which is likely to be due to the use of PSI-BLAST score profiles (we used frequency profiles derived from the HSSP database in the previous study). When the values obtained from the contact number prediction are compared to the native RWCOs, the highest correlation is 0.50 with the optimal half window size of $M = 4$ (Table
Case C). Although the correlation of 0.50 is statistically significant, the value is much lower than the one obtained for the proper prediction of RWCO, $\text{Cor}_p \approx 0.59$ (Table 2, Case A). For the “prediction” in the opposite direction, that is, when the values obtained from the RWCO prediction are compared to the native contact numbers, the correlation is as high as 0.62 with the optimal half window size of $M = 4$ (Table 2, Case D). Again, this value, though statistically significant, is lower than the proper contact number prediction ($\text{Cor}_p \approx 0.70$). Interestingly, for the Cases C and D in Table 2 the optimal half window sizes coincide ($M = 4$). Therefore, it is expected that the contact number and RWCO are very closely related with each other in terms of the short-range pattern of the local amino acid sequence. In other words, the distinction between the contact number and RWCO originates from the interactions of longer range.

To further clarify the correlation between RWCO and contact number predictions, we compared the regression parameters $C_{m,a}$ for RWCO and contact number predictions up to the half window size of $M = 9$ (Figure 5). It can be clearly seen that the both sets of regression parameters very significantly correlate (correlation of $> 0.7$) with each other within the window positions of $-4 \leq m \leq 4$ (Figure 5), which confirms the above observation (Table 2, Cases C and D).

**Perspective for improving prediction accuracy**

The method for predicting RWCOs from amino acid sequence developed in this paper is a very primitive one. While the correlation of 0.59 between the native and predicted RWCOs is significant, it is not as high as 0.70 in the case of the contact number prediction (Table 2) based on the same linear regression scheme. Furthermore, the agreement of absolute RWCO values is relatively poor, especially so for RWCOs of large values. As mentioned above, inclusion of many-body effects seems mandatory for better RWCO prediction. A popular method for dealing with many-body terms is artificial neural networks. Other non-linear regression
schemes such as radial basis or support vector regressions can be also applicable. Neural network methods as well as a support vector regression method have been successfully applied to real value prediction of solvent accessibility\textsuperscript{13,14,15}. Solvent accessibility is closely related to the hydrophobicity of amino acids, and hence is likely to be related to the RWCO. Thus, we can expect such non-linear regression approaches may be also useful for predicting RWCO. However, since the RWCO prediction requires rather long segment of local amino acid sequence (half window size of $M = 26$), straightforward application of non-linear regression methods requiring a great number of parameters may not work. The number of parameters must be somehow reduced. How to extract essential parameters for RWCO prediction is left for future studies.

An alternative route to the improved accuracy is to properly treat the large deviation of RWCOs along the amino acid sequence. For the contact number, its average over a local segment tends to be close to the average over the whole sequence, whereas, for the RWCO, such is not the case. For example, for the SCOP domain d1a9xb1 (Figure 3C), the average contact number for the whole domain, for residues 1 to 20, and for residues 51 to 70 are, respectively, 25.5, 28.4, and 26.6, whereas the corresponding averages of the RWCOs are 8.0, 14.3, and 4.9, respectively. Since the present method is based on the globally normalized RWCO (Eq. 3), such large deviations are difficult to handle. If this limitation is overcome, better prediction accuracy may be obtained.

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The list of the SCOP domain identifiers used in the present study, and the opti-
mal parameter sets are available at the URL http://maccl01.genes.nig.ac.jp/~akinjo/rwco/.

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Table 1: Distribution of $Cor_p$ for each SCOP class$^a$.

| range$^b$ $(Cor_p)$ | a   | b     | c     | d     | e   |
|---------------------|-----|-------|-------|-------|-----|
| (-1,0.2]           | 4(3)| 1(0.6)| 7(4)  | 2(0.8)| 0   |
| (0.2,0.4]          | 23(14)| 17(10)| 14(8) | 22(9) | 1(5) |
| (0.4,0.6]          | 61(38)| 54(33)| 55(33)| 72(30)| 11(61)|
| (0.6,0.8]          | 73(45)| 86(52)| 82(49)| 136(57)| 6(33)|
| (0.8,1.0]          | 1(0.6)| 6(4)  | 8(5)  | 8(3)  | 0   |
| total              | 162| 164   | 166   | 240   | 18  |

$^a$ The number (percentage in the parentheses) of occurrences of $Cor_p$ for the proteins in the test sets, classified according to the SCOP database.

$^b$ The range “$(x, y]$” denotes $x < Cor_p \leq y$.

$^c$ a: all-$\alpha$, b: all-$\beta$, c: $\alpha/\beta$, d: $\alpha + \beta$, e: multi-domain.
Table 2: Cross-prediction between residue-wise contact orders and contact numbers.

| Case | Train\(^a\) | Test\(^b\) | \(M\(^c\)\) | \(Cor_p\) | \(DevA_p\) |
|------|-------------|-------------|-------------|-----------|-----------|
| A    | RWCO       | RWCO       | 26          | 0.59      | 1.03      |
| B    | CN         | CN         | 9           | 0.70      | 0.803     |
| C    | CN         | RWCO       | 4           | 0.50      | N.A.\(^d\) |
| D    | RWCO       | CN         | 4           | 0.62      | N.A.\(^d\) |

\(^a\)Target values for which the regression parameters were trained. “RWCO” and “CN” indicate that the regression parameters were trained to fit the residue-wise contact orders and contact numbers, respectively.

\(^b\)Target values for which the “prediction” was applied. “RWCO” and “CN” indicate that predicted values were compared with the native residue-wise contact orders and native contact numbers, respectively.

\(^c\)Optimal half window size for the prediction.

\(^d\)Not applicable because the ranges of RWCO and CN values are different.
Figure 1: Prediction accuracy as a function of window size. (A) The correlation coefficient ($Cor_P$) between the native and predicted RWCO, averaged over the test set proteins. (B) Deviation of the predicted RWCO from the native one ($Dev_A_P$), averaged over the test set proteins.
Figure 2: $Cor_p$ plotted against chain length. Each point represents a protein in one of the test sets.
Figure 3: Examples of prediction. Red: native RWCO; Green: predicted RWCO.
(A) SCOP domain d1a6m (myoglobin, all-α), $Cor_p = 0.73$, $DevA_p = 0.75$; 
(B) SCOP domain d1ifra (Lamin A/C globular tail domain, all-β), $Cor_p = 0.72$, $DevA_p = 0.87$; 
(C) SCOP domain d1a9xb1 (Carbamoyl phosphate synthetase, small subunit N-terminal domain, α/β), $Cor_p = 0.72$, $DevA_p = 0.81$. 
Figure 4: $C_{m,a}$ for each amino acid type ($a$) as a function of the window position ($m$).
Figure 5: Correlation between the regression parameters $C_{m,a}$ for contact number and RWCO predictions for each window position. The horizontal axis is the window position $m$ in the local sequence. The vertical axis is the correlation coefficient between the regression parameters $C_{m,a}$ for RWCO prediction and those for contact number prediction at the window position $m$. 