A Tensor-Free Method for the Structural and Dynamical Refinement of Proteins using Residual Dipolar Couplings

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ABSTRACT: Residual dipolar couplings (RDCs) are parameters measured in nuclear magnetic resonance spectroscopy that can provide exquisitely detailed information about the structure and dynamics of biological macromolecules. We describe here a method of using RDCs for the structural and dynamical refinement of proteins that is based on the observation that the RDC between two atomic nuclei depends directly on the angle ϑ between the internuclear vector and the external magnetic field. For every pair of nuclei for which an RDC is available experimentally, we introduce a structural restraint to minimize the deviation from the value of the angle ϑ derived from the measured RDC and that calculated in the refinement protocol. As each restraint involves only the calculation of the angle ϑ of the corresponding internuclear vector, the method does not require the definition of an overall alignment tensor to describe the preferred orientation of the protein with respect to the alignment medium. Application to the case of ubiquitin demonstrates that this method enables an accurate refinement of the structure and dynamics of this protein to be obtained.

INTRODUCTION

Residual dipolar couplings (RDCs) have emerged as one of the most useful parameters in biomolecular nuclear magnetic resonance (NMR) spectroscopy.1−12 They have been applied to a wide range of different problems, ranging from the determination of the structure of proteins,1−8 nucleic acids,9−12 and carbohydrates,13−16 to the characterization of their dynamics.17−21

The RDC between two atomic nuclei depends on the angle between the internuclear vector and the external magnetic field.33,34 In isotropic media RDCs average to zero because of orientational averaging, but when the rotational symmetry is broken, either through the introduction of an alignment medium,33,34 or for molecules with highly anisotropic paramagnetic susceptibility,35 RDCs become measurable. In order to translate the information provided by RDCs into molecular structures, several accurate methods for calculating the RDCs corresponding to given conformations have been developed.36−44 These methods are based on the introduction of an alignment tensor to describe the preferential orientation of a molecule with respect to the alignment medium.1,14,45,46

In addition to their usefulness in protein structure determination, RDCs can also be used for characterizing the dynamics of proteins. These NMR parameters, however, tend to have a strong structural dependence and, hence, to experience large fluctuations as a protein explores its conformational space,36,46 which is an aspect that complicates the extraction of the information about dynamics from them. When conformational fluctuations of large amplitude are present, even the most accurate methods for calculating the RDCs for a given structure36−44 may not provide values that can be expected to match the experimental ones. A close agreement between calculated and experimental RDCs can in these cases be obtained by averaging the calculated RDCs over an ensemble of structures representing the motions of the protein.17−28,44,49−51

As the calculation of the alignment tensor requires procedures of a certain complexity, which in some cases, in particular when electrostatic alignment media are used, can be very challenging,36−44 it is interesting to explore alternative “tensor-free” methods that do not require the introduction of an alignment tensor.52 For this purpose, here we describe a method for protein structural and dynamical refinement based on the direct dependence of the RDC between two atomic nuclei on the angle ϑ between the internuclear vector and the external magnetic field. In this protocol, called the “ϑ method”, one introduces in the refinement protocol a structural restraint that minimizes the deviation from the experimental and calculated values of the angle ϑ.

The main advantage of the ϑ method is its simplicity. The relationship between an RDC and the structure of a protein is described in a straightforward manner by the orientation of the corresponding internuclear vector with respect to the external magnetic field (Figure 1). In this sense, the ϑ method requires just the calculation of the angles ϑ for the interatomic bonds for which RDCs have been measured, and not that of the overall alignment tensor. We illustrate the ϑ method by presenting its application to the refinement of the structure and dynamics of the protein ubiquitin, showing that it leads to results essentially as accurate as those obtained by standard NMR approaches.
vector with respect to the external magnetic field caused by the RDCs to recapture the full changes in the alignment tensor during the conformational fluctuations of large amplitude.

In the presence of conformational fluctuations, it is more effective to use structure-based methods. In this case, each member in a structural ensemble can be associated with its own alignment tensor without the need of using experimental data. In practice, the averaging in eq 1 is carried out both over the external degrees of freedom, which involve rotations and translations, and the internal ones, which involve conformational fluctuations of a protein.

The Method of Structural Refinement. As mentioned above, it is not necessary to recast eq 1 in the framework of the internal coordinates and hence as a function of an alignment tensor, although in this case, one should consider just 5 degrees of freedom for the rotations and 3 further degrees of freedom for the translations of a protein molecule. More generally, if a protein undergoes conformational fluctuations, it is still possible to define an alignment tensor, although in this case the averaging has to be carried out not only over the rotations and translation of the molecule with respect to the alignment medium but also with respect to its internal degrees of freedom.

The alignment tensor of a given protein conformation can be obtained through fitting procedures, such as the singular-value decomposition (SVD) method, in which the alignment tensor is chosen to optimize the agreement between calculated and experimental RDCs. Alternatively, the alignment tensor can be determined by structure-based procedures in which this quantity is calculated on the basis of the shape and charge of the protein molecule and the alignment medium without reference to experimentally measured RDCs.

These two approaches are generally applicable to different situations. This aspect can be understood in particular in the presence of conformational fluctuations of large amplitude. In this case, the calculation of the average RDCs corresponding to an ensemble of conformations involves the definition of a different alignment tensor for each conformation in the ensemble. In approaches in which the RDCs are fitted to a structure, to simplify the calculations, one can assume that all the conformations in the ensemble have the same alignment tensor, which, however, is often not an accurate approximation. Alternatively, to achieve greater accuracy, one can obtain the alignment tensor of each individual conformation by a separate fitting to the experimental RDCs. In this case, however, an impractically large number of experimental RDCs is required in order to avoid overfitting. Therefore, fitting methods are at risk of failing to capture the full changes in the alignment tensor during the conformational fluctuations.

Calculation of RDCs Using Alignment Tensor Methods. When a structural model of the protein is available, there are several ways to carry out the average in eq 1 to estimate the corresponding RDCs. The most common approaches involve the definition of an alignment tensor, either explicitly or implicitly, a procedure that is particularly convenient if a protein populates a rigid structure, so that the only important degrees of freedom in eq 1 concern the relative orientation of the molecule with respect to the alignment medium. In this case, one should consider just 5 degrees of freedom for the rotations and 3 further degrees of freedom for the translations of a protein molecule. More generally, if a protein undergoes conformational fluctuations, it is still possible to define an alignment tensor, although in this case the averaging has to be carried out not only over the rotations and translation of the molecule with respect to the alignment medium but also with respect to its internal degrees of freedom.

The advantage of using the definition of the RDCs without recasting the equations in a tensor-dependent way is that of removing the need of calculating the alignment tensor, either implicitly by means of the single value decomposition or
explicitly by modeling the alignment media, which are procedures that add approximations as well as computational burden. The method discussed in this work does not require the knowledge of the alignment tensor, and its results do not depend on the properties (as for example the axial symmetry or the rhombicity) of the alignment tensor itself.

In order to implement this strategy for structural refinement, we included an additional term to the CHARMM22 force field\(^6\) using PLUMED \(^6\) to maximize the correlation, \(\rho\), between the calculated, \(D_{\text{calc}}\), and the experimental, \(D_{\text{exp}}\), RDCs

\[
V_\rho = -K_\rho \left[ \rho (D_{\text{calc}} - D_{\text{exp}}) - 1 \right] 
\]

Once a high correlation is obtained, it is possible to find the scaling factor for the RDCs as the slope of the line that fits \(D_{\text{exp}}\) as a function of \(D_{\text{calc}}\) and hence apply a simpler restraining potential of the form

\[
E_\rho = K_\rho \sum (D_i - D_i^{\text{exp}})^2 
\]

where \(i\) runs over the experimental RDCs. In the implementation presented in eq 2, the \(\vartheta\) method can be applied to multiple bonds measured in a single alignment medium. Subject to further developments, however, it may be possible to extend its use to multiple alignment media.

In the calculations, we also added a potential on the \(\omega\) angles of the peptide bonds

\[
V_\omega = \frac{K_\omega}{2} \left[ 1 + \cos(\omega - \omega_{\text{ref}}) \right] 
\]

with \(K_\omega\) set to 2500 kJ/mol. This term was introduced because in unrestrained simulations of ubiquitin we noticed that using the CHARMM22 force field resulted in a distribution of the values of the \(\omega\) angles slightly wider than expected from X-ray structures in the PDB.

**The Method of Dynamical Refinement.** In order to extract the information about dynamics provided by RDCs, we incorporated them as replica-averaged structural restraints in molecular dynamics simulations.\(^6\) This approach generates an ensemble of conformations consistent with the maximum entropy principle.\(^6\) In this view, the generated ensemble is the most probable one, given the force

| Table 1. Assessment of the Structure of Ubiquitin (2MOR) Obtained Using the \(\vartheta\) Method in Comparison with High-Resolution X-ray (1UBQ\(^{70}\)) and NMR (1D3Z\(^{77}\)) Structures* |
|-----------------------------------------------|-------------------|-------------------|
|                                | 1UBQ (X-ray)       | 1D3Z (4159 restraints) | 2MOR (381 restraints) |
| Q Factor for the RDCs\(^*\) Used in This Work as Restraints (SVD) | 0.16/0.21 (0.05)/0.19 | 0.13/0.13 (0.12)/0.24 | 0.16/0.29 |
| N–H (AA 1–70/1–76)          | 0.21 ± 0.03        | 0.17 ± 0.05        | 0.19 ± 0.04 |
| Ca–Hα (AA 1–70/1–76)        | 0.29 ± 0.06        | 0.29 ± 0.07        | 0.29 ± 0.07 |
| Q Factor for Squalamine RDCs\(^\text{a}\) | 0.19/0.14 (0.05)/0.19 | 0.36/0.33 (0.20)/0.23 | 0.22/0.31 (0.12)/0.24 |
| N–H (AA 1–70/1–76)          | 0.21/0.29 (0.14)/0.24 | 0.23/0.40 (0.36)/0.37 | 0.22/0.31 (0.12)/0.24 |
| Ca–Hα (AA 1–70/1–76)        | 0.39/0.42 (0.26)/0.40 | 0.36/0.43 (0.20)/0.23 | 0.22/0.31 (0.12)/0.24 |
| Ca–C (AA 1–70/1–76)         | 0.25/0.32 (0.14)/0.28 | 0.25/0.37 (0.25)/0.37 | 0.22/0.31 (0.12)/0.24 |
| C–N (AA 1–70/1–76)          | 0.22/0.33 (0.20)/0.28 | 0.25/0.37 (0.25)/0.37 | 0.22/0.31 (0.12)/0.24 |
| C–H (AA 1–70/1–76)          | 0.38/0.47 (0.30)/0.51 | 0.28/0.43 (0.28)/0.43 | 0.22/0.31 (0.12)/0.24 |

*Q factors were obtained using the SVD method to back-calculate the RDCs from the structures. Numbers in parentheses indicate parameters used as restraints in the structure determination protocol; Q factors are given separately for the protein without the C-terminal tail (AA 1–70) and the full-length protein (AA 1–76). The PROCHECK method\(^8\) was used to quantify the structural quality for backbone (\(\varphi/\varphi\)) and side-chain (\(\chi_1,\chi_2,\omega\)) dihedral angles and hydrogen-bond geometries (H bonds). Scalar coupling through hydrogen bond have been calculated using a simple geometric relation (see text). NOE have been calculated using the PROSESS web server.\(^7\) Backbone chemical shifts are calculated with SHIFTX2\(^8\) and methyl \(^1\)H chemical shifts using CH3Shifts\(^8\).
field and the experimental data included, that reproduces at the same time the conformational dynamics of the system under study and the distribution of the orientations with respect to the alignment media employed to measure the RDCs. To this effect, in eq 3 we averaged the calculated RDCs over 8 replicas of the protein molecule. In this respect, the structural refinement procedure can be seen as a limiting case in which the dynamics can be well-represented by a single average structure. In the case of the refinement of the dynamics, the additional restraint in eq 4 was not added.

## RESULTS AND DISCUSSION

**Refinement of the Structure of Ubiquitin Using the θ Method.** To illustrate the use of the θ method, we applied the structure refinement protocol described in the Method section starting from an X-ray structure of ubiquitin (1UBQ). We selected a set of experimental RDCs measured in a liquid crystalline phase for the N–H, Ca–Ha, Ca–C′, C′–N, and C′–H bond vectors; only the data for the first 70 residues were used because the last 6 residues belong to a flexible tail (i.e., in total, we used 381 restraints, see Table 1). We prepared the system using GROMACS, adding hydrogen atoms and explicit solvent. We used the CHARMM22 force field, a cubic box of 6.5 nm of side with 8700 TIP3P water molecules. A time step of 2 fs was used together with LINCS constraints. The van der Waals interactions were treated with the particle mesh Ewald method. All simulations were carried out keeping the volume fixed and by thermostating the system with the Bussi thermostat.

The energy of the system was first minimized without accounting for the additional term. Then the temperature was raised to 300 K by a linear increase in 300 ps. In this phase, together with the temperature, the RDC restraint constant $K_θ$ was also increased linearly from 100 to 5000 kJ/mol. The system was then evolved for further 200 ps at constant temperature. After that, $K_θ$ was further increased linearly from 5000 to 15000 kJ/mol in 200 ps. Then the simulations were run for further 1.3 ns. In addition to the RDCs restraint, we have also employed a restraint on the $ω$ angles of the peptide bonds as illustrated in eq 4 in Methods. At the end of the 2 ns simulation, the correlation between experimental and calculated RDCs was about 0.995 and it was then possible to evaluate the scaling factor using a linear fit of the data. In this way, it was possible to directly compare the values of the calculated RDCs with the corresponding experimental values using the Q factor

$$Q = \sqrt{\frac{\sum (D_{calc} - D_{exp})^2}{\sum D_{exp}^2}}$$

where $D_{calc}$ and $D_{exp}$ are the calculated and experimental RDCs, respectively. This value is comparable with that calculated using the SVD method as implemented in PALES (Figure 2, red curve). We note that since the SVD method is insensitive to the overall rotations, the 300 ps transient time exhibits lower Q values (Figure 1, red curve).

To further test the θ method, we applied the same protocol starting from a poor quality structure at about 2.5 Å from the reference X-ray structure of ubiquitin (1UBQ shown in turquoise in Figure 3). We found that after about 4.5 ns the RMSD with 1UBQ became comparable with that of the high-resolution reference NMR structure (1D3Z); the green band indicates the RMSD between the 10 models in the 1D3Z file and the 1UBQ reference structure. For comparison, we show the RMSD resulting from an unrestrained simulation using the same force field but without the RDC restraints (shown in yellow).

![Figure 3](image)

**Figure 3.** Refinement using the θ method from a starting structure of poor quality. Starting from a structure (shown in green) at about 2.5 Å from a reference X-ray structure of ubiquitin (1UBQ shown in turquoise), we applied the θ method, finding that after about 4.5 ns, the RMSD with 1UBQ (shown in blue) became comparable with that of the high-resolution reference NMR structure (1D3Z); the green band indicates the RMSD between the 10 models in the 1D3Z file and the 1UBQ reference structure. For comparison, we show the RMSD resulting from an unrestrained simulation using the same force field but without the RDC restraints (shown in yellow).
SVD calculation for RDCs have been performed with exp(−θHO/Å)cos2θ, where θ represents the HO–C angle. Methyl 1H chemical shifts are calculated using CH3Shift,38 and SVD calculation for RDCs have been performed with PALES.36,41

Overall, the structure that we obtained using the θ method showed a comparable quality with respect to 1UBQ and 1D3Z (Table 1) and represents an improvement over 1UBQ in terms of agreement with several independent experimental measurements, indicating that the refinement protocol that we used is effective in providing structures of high quality.

Refinement of the Dynamics of Ubiquitin Using the θ Method. To illustrate the use of the θ method within a dynamical refinement protocol, we use the same simulation set up described for the structure refinement protocol, with the difference that the RDCs are now calculated as averages over 8 replicas of the protein molecule (see Methods) and that the simulations were performed at constant temperature (300 K). We used the same set of experimental RDCs described above for the structural refinement (381 RDCs) (i.e., N–H, Ca–Hα, Cα–C′, C′–N, and C′–H bond vectors measured in a liquid crystalline phase77), now including also the data for the last 6 residues belonging to the C-terminal flexible tail, and generated an ensemble of structures (the “θ 5-bonds” ensemble) by maximizing the agreement between experimental and back-calculated RDCs.

Eight starting structures for the replica-averaged RDCs restrained simulation were generated by running eight 1 ns simulations from the solvated 1UBQ structure without employing experimental restraints. During the first 1 ns in the replica-averaged restrained simulation, the RDCs restraint constant Kθ was increased linearly from 100 kJ/mol to 50000 kJ/mol, applying the restraint in the form of a correlation (see eq 2). The simulation readily reached a region of the conformational space characterized by small violations of the RDC restraints, as illustrated in the case of the N–H RDCs in Figure 5. We evaluated the scaling factor using a linear fit of the experimental and calculated RDCs and switched the restraint in the form of eq 3. We then continued the simulations for another 100 ns per replica to sample the conformational space compatible with the averaged restraints and thus generate an ensemble of conformations consistent with the RDCs. As ubiquitin is a rather rigid molecule in its native state, the structures in the ensemble have a narrow distribution of pairwise root-mean-square (RMS) distances (Figure 6).

In order to explore the robustness of the method, we then repeated the calculations by using only two bond vectors (N–H and Ca–Hα), obtaining a second ensemble of structures (the “θ 2-bonds” ensemble), which was structurally quite close to the “θ 5-bonds” ensemble (Tables 2 and 3).

Validation of the Dynamics of Ubiquitin. To assess the quality of the θ 5-bonds and the θ 2-bonds ensembles, we compared them with other existing high-resolution ensembles in the PDB, including three ensembles determined using RDC restraints (2LJS,44 2KOX,21 and 2K3920), with an ensemble determined using NOEIs and S2 order parameters (2NR283).
and with an ensemble (MD) obtained using a control simulation with the same procedure of the \( \vartheta \) method but without RDC restraints (Tables 2 and 3).

We then calculated the Q factors for independent sets of RDCs, finding that both the \( \vartheta \) 5-bonds and the \( \vartheta \) 2-bonds ensembles reproduce quite well independent measurements (Table 2). Indeed, they satisfy these RDCs in a comparable manner to the high-quality ensembles described above, which in many cases used these RDCs as restraints in the calculations. Further, we used the PROCHECK method78 (Table 3) to quantify the structural quality for backbone \((\phi/\psi)\) and side-chain \((\chi_1, \chi_2, \omega)\) dihedral angles and hydrogen-bond geometries \((\text{H bonds})\). The two ensembles obtained by using 5 bonds \((\vartheta \ 5\text{-bonds})\) and 2 bonds \((\vartheta \ 2\text{-bonds})\) are compared with three ensembles in the PDB determined using RDC restraints \((2LJ5, \ 2KOX, \ \text{and} \ 2K39)\), with an ensemble determined using NOEs and S2 order parameters \((2NR2)\) and with an ensemble \((\text{MD})\) obtained using a control simulation with the same procedure of the \( \vartheta \) method but without RDC restraints.

### Table 3. Assessment of the Quality of the Structures Comprising the Ensemble Representing the Dynamics of Ubiquitin Obtained Using the \( \vartheta \) Method

<table>
<thead>
<tr>
<th>Method</th>
<th>Structure Quality</th>
<th>Check</th>
</tr>
</thead>
<tbody>
<tr>
<td>2LJ5</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2KOX</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2K39</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>( \vartheta ) 5-bonds</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>( \vartheta ) 2-bonds</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>MD</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2NR2</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

The PROCHECK method78 was used to quantify the structural quality for backbone \((\phi/\psi)\) and side-chain \((\chi_1, \chi_2, \omega)\) dihedral angles and hydrogen-bond geometries \((\text{H bonds})\). Numbers in parentheses indicate parameters used as restraints in the ensemble determination protocol.

### CONCLUSIONS

We have presented a method of using RDCs for structural and dynamical refinement of proteins. This method is not based on the introduction of an alignment tensor but on the direct use of the information provided by RDCs about the angles between the internuclear vectors and the external magnetic field. Application to the case of ubiquitin has illustrated that this approach can achieve a structural accuracy comparable to that of other more standard NMR procedures. We anticipate that tensor-free approaches of the type discussed in this work will be

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**Figure 6.** Representation of the structural heterogeneity of the \( \vartheta \ 5\text{-bonds} \) ensemble of ubiquitin using the distribution of the root-mean-square (RMS) distances between pairs of structures in the ensemble. The ensemble is obtained by collecting the conformations generated during the sampling carried out with a 8-replica averaging of the RDCs to obtain the structural restraints \((\text{see Methods})\).
Table 4. Assessment of the Quality of the Ensemble of Structures Representing the Dynamics of Ubiquitin Obtained Using the ℓ Method\(^{a}\)

<table>
<thead>
<tr>
<th></th>
<th>2LJ5</th>
<th>2K0X</th>
<th>2K39</th>
<th>θ (5-bonds)</th>
<th>θ (2-bonds)</th>
<th>MD</th>
<th>2NR2</th>
</tr>
</thead>
<tbody>
<tr>
<td>2JINC-(δ) RMSD (Hz)</td>
<td>0.12</td>
<td>0.12</td>
<td>0.14</td>
<td>0.08</td>
<td>0.09</td>
<td>0.11</td>
<td>0.14</td>
</tr>
<tr>
<td>2JINC-(δ) RMSD (ppm)</td>
<td>0.78</td>
<td>0.88</td>
<td>0.82</td>
<td>0.88</td>
<td>0.86</td>
<td>0.83</td>
<td>0.83</td>
</tr>
<tr>
<td>θ violations</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>(0)</td>
</tr>
<tr>
<td>(ΔCα) RMSD (ppm)</td>
<td>0.5</td>
<td>0.6</td>
<td>0.6</td>
<td>0.5</td>
<td>0.5</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>(ΔCβ) RMSD (ppm)</td>
<td>0.7</td>
<td>0.7</td>
<td>0.8</td>
<td>0.7</td>
<td>0.7</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>(ΔC) RMSD (ppm)</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>(Δ) RMSD (ppm)</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>(δ) RMSD (ppm)</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>methyl RMSD (ppm)</td>
<td>1.9</td>
<td>1.9</td>
<td>2.0</td>
<td>1.9</td>
<td>2.2</td>
<td>2.4</td>
<td>1.9</td>
</tr>
</tbody>
</table>

\(\text{We considered the violations of hydrogen-bond } J \text{ couplings (}\left\langle \delta J_{\text{INC}} \right\rangle\text{), both in terms of root mean square deviations (RMSD in Hz) and of coefficient of correlation (R) between experimental and calculated } J \text{ couplings, the violations of NOE-derived distances, and violations of experimental and calculated chemical shifts (RMSD in ppm). For the 2NR2 ensemble 1320 NOE restraints were used in the ensemble determination protocol.}\)

useful in situations where the calculation of the alignment tensors is challenging, as, for example, in the case of highly charged alignment media.

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**Notes**

The authors declare no competing financial interest.

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