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研究課題名（和文）Use of contact prediction-based restraints for protein structure determination from sparse NMR data

研究課題名（英文）Use of contact prediction-based restraints for protein structure determination from sparse NMR data

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研究成果の概要（和文）：本課題で開発した新規NMR自動解析プログラム(ARTINA)を用いることにより、多次元NMRスペクトルからピークリスト取得、化学シフト帰属、および蛋白質立体構造決定の一連の流れを完全に自動化することに成功した．ARTINAは，AlphaFold2構造の情報も入力可能であり，構造情報は化学シフトの近似予測やNOESYスペクトル予測に利用できるため，構造を考慮しない場合よりも少ないデータから信頼性の高い解析が可能であることが示された．ARTINAアルゴリズムは、NMRtistウェブサーバーを介して利用可能であり，数時間の計算時間で，NMRスペクトルを自動解析し蛋白質の最終構造を出力できる．

研究成果の学術的意義や社会的意義
Nuclear magnetic resonance spectroscopy (NMR) provides detailed information on structure, dynamics and interactions of proteins. The method developed in this project will accelerate virtually any biological NMR studies that require the analysis of protein NMR spectra and chemical shift assignments.

研究成果の概要（英文）：We have incorporated the use of protein structures predicted by AlphaFold2 into our fully automated NMR spectra analysis algorithm ARTINA, which yields peak lists, chemical shift assignments, and three-dimensional protein structures directly from a set of multidimensional NMR spectra without any manual work. The AlphaFold2 structures can be used in ARTINA for the structure-based prediction of approximate chemical shifts and for generating the cross peaks expected in NOESY-type spectra. It could be shown that the AlphaFold2 structures enable to obtain reliable chemical shift assignments from smaller sets of NMR spectra than without structures. Thus, NMR measurement times can be significantly reduced and the NMR studies of proteins becomes more efficient. The ARTINA algorithm has been made available in the NMRtist webserver that allows scientists to obtain assignments and structures of proteins within a few hours of computation time rather than weeks or months of manual analysis.

研究分野：Biophysical Chemistry

キーワード：machine learning　NMR　protein structure　automated assignment

１．研究開始当初の背景

Nuclear magnetic resonance spectroscopy (NMR) is a key analytical technique that provides detailed information on structure, dynamics, and interactions of proteins. These data can be obtained simultaneously for a large number of individual atom positions using the intrinsically present probes of nuclear spins. To achieve this atomic resolution, it is necessary to attribute resonance frequencies of nuclear spins, expressed as chemical shifts, to individual atoms in the protein. This chemical shift assignment is a key task in most NMR studies of proteins. It is generally achieved by recording and analyzing a set of multi-dimensional NMR spectra. Each cross peak in an *n*-dimensional spectrum correlates *n* atoms with each other, and alignments among the cross peaks make it possible to uniquely link chemical shift values to individual atoms in the chemical structure of the protein. This process is generally demanding in terms of NMR measurements and spectra analysis. Most of the spectrometer measurement time in a biomolecular NMR project is frequently spent to measure spectra for the chemical shift assignment, which are not of direct use to the question at stake, such as, for instance, elucidating dynamics or interactions of the protein. The same holds for the time spent by the spectroscopist: finding chemical shift assignments is time-consuming and requires expertise.

To change this situation by accelerating NMR chemical shift assignment, one should reduce the number of spectra required and automate their analysis without compromising the reliability of the results. In this project, we developed a method that achieves this by exploiting recent advances in machine learning and by efficiently incorporating into the assignment process the information contained in three-dimensional (3D) protein structures. The latter serve to replace information that would otherwise have to be gathered from additional NMR spectra.

Knowledge of the 3D structure of a protein can support the automated chemical shift assignment in mainly two ways: by more realistic prediction of the expected cross peaks in NOESY spectra and through structure-based predictions of chemical shift values. This has become particularly relevant because with AlphaFold2 accurate predictions of the 3D structure are now generally available for most proteins.

２．研究の目的

Studying structures of proteins and ligand-protein complexes is one of the most influential endeavors in molecular biology and rational drug design. All key structure determination techniques, X-ray crystallography, electron microscopy, and NMR spectroscopy, have led to remarkable discoveries, but suffer from their respective experimental limitations. NMR can elucidate structures and dynamics of small and medium size proteins in solution and even in living cells. However, the analysis of NMR spectra and the resonance assignment, which are indispensable for NMR studies, remain time-consuming even for a skilled and experienced spectroscopist. The problem has sparked research towards automating different tasks in NMR structure determination, including peak picking, resonance assignment, and the identification of distance restraints. This enabled semi-automatic but not yet unsupervised automation of the entire NMR structure determination process, except for a very small number of favorable proteins.

The advance of machine learning techniques now offers unprecedented possibilities for reliably replacing decisions of human experts by efficient computational tools. We recently developed a machine learning-based method, ARTINA, to perform completely automated analysis of protein NMR data within hours after completing the measurements. Using only NMR spectra and the protein sequence as input, ARTINA delivers signal positions, resonance assignments, and structures strictly without human intervention. Through its implementation in the NMRtist website (Figure 1), ARTINA can be used by non-experts, reducing the effort for a protein assignment or structure determination by NMR essentially to the preparation of the sample and the spectra measurements.

The purpose of this project was to further improve the performance of ARTINA by combining it with protein structure prediction by AlphaFold2 in order to render the NMR analysis of proteins more efficient and reliable.

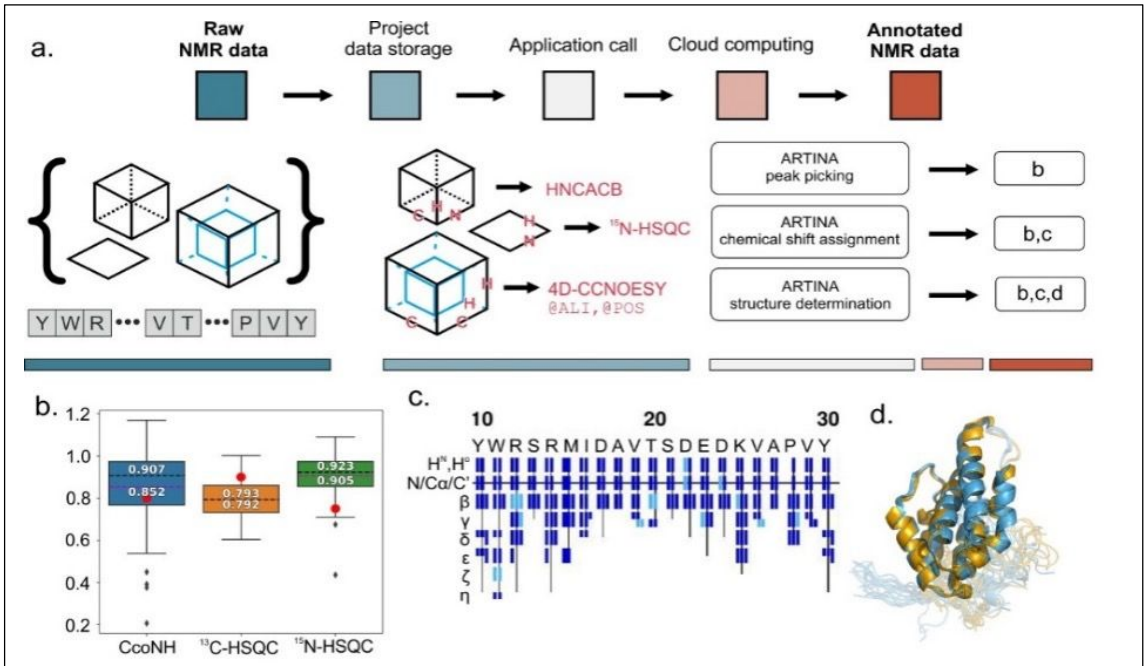

Figure 1. NMRtist data analysis workflow. **a**. A set of raw 2D/3D/4D NMR spectra and the protein sequence are uploaded to the project data storage as input for application calls, yielding outputs b-d. **b.** Example figure generated by the ARTINA peak picking application. It presents F_1 scores of automated peak picking (red dots) in comparison with those of all spectra of the same type in a benchmark of 1329 spectra (box plot). **c.** Example figure generated by the ARTINA chemical shift assignment application. Each column corresponds to a single amino acid with color-coded confidence of automatically assigned shift values (high/low confidence in dark/light blue, respectively). **d**. Visualization of protein structures generated by the ARTINA structure determination application. Differences between structure candidates indicate either flexible regions or uncertainty in the structure determination.

3．研究の方法

The original ARTINA algorithm uses as input exclusively a set of multidimensional NMR spectra and the amino acid sequence of the protein. In this project, we extended ARTINA to handle additional types of input data, in particular 3D structures predicted by AlphaFold2. ARTINA employs the FLYA algorithm to assign chemical shifts. FLYA uses as mandatory input the protein sequence and peak lists from a set of NMR spectra. These can be complemented by 3D structures and chemical shift information.

3D structures were obtained from protein sequences by AlphaFold2. They can be used directly by FLYA for generating the cross peaks that are expected in NOESY spectra. An expected NOESY cross peak is generated whenever the corresponding distance is shorter than a given cutoff in a given minimal number of conformers in the structure bundle. In the absence of an input structure, FLYA applies this criterion to an internally generated bundle of random structures, i.e., structures with correct covalent geometry but random torsion angle values that are only minimized to avoid steric clashes. Consequently, only expected cross peaks that correspond to short-range distances (within a residue or between neighboring residues) will be obtained because the distance between two atoms located far apart in the protein sequence are highly unlikely to be consistently short in all members of the random structure bundle. In contrast, if a well-defined structure is provided to FLYA, also medium-range and long-range expected NOESY cross peaks will be generated, which corresponds better to the situation in the experimental spectra where such peaks are observed.

Input chemical shift information for FLYA may comprise statistical information on the distribution of chemical shifts, which, if available, replaces the default statistics used by FLYA as a priori information for the chemical shift assignment. Chemical shift distributions are modelled in FLYA as normal distributions defined by their mean and standard deviation. Using structure-based chemical shift prediction, one can in many cases obtain chemical shift distributions that are more accurate (i.e., have a mean value closer to the actual chemical shift value) and more precise (i.e., have a smaller standard

deviation then the general BMRB distribution), and thus help FLYA in determining reliable assignments. For this, it is not necessary that the chemical shift prediction algorithm provides the correct value with high precision. The predicted chemical shift values are rather used in FLYA to contract the search space in order to facilitate the assignment by decreasing the number of assignment possibilities that must be considered during combinatorial optimization. All chemical shift predictions used in this project were obtained for backbone H^N, N, C^α C^β, and C' atoms by the state-of-the-art UCBShift method using as input 3D structures predicted by AlphaFold2.

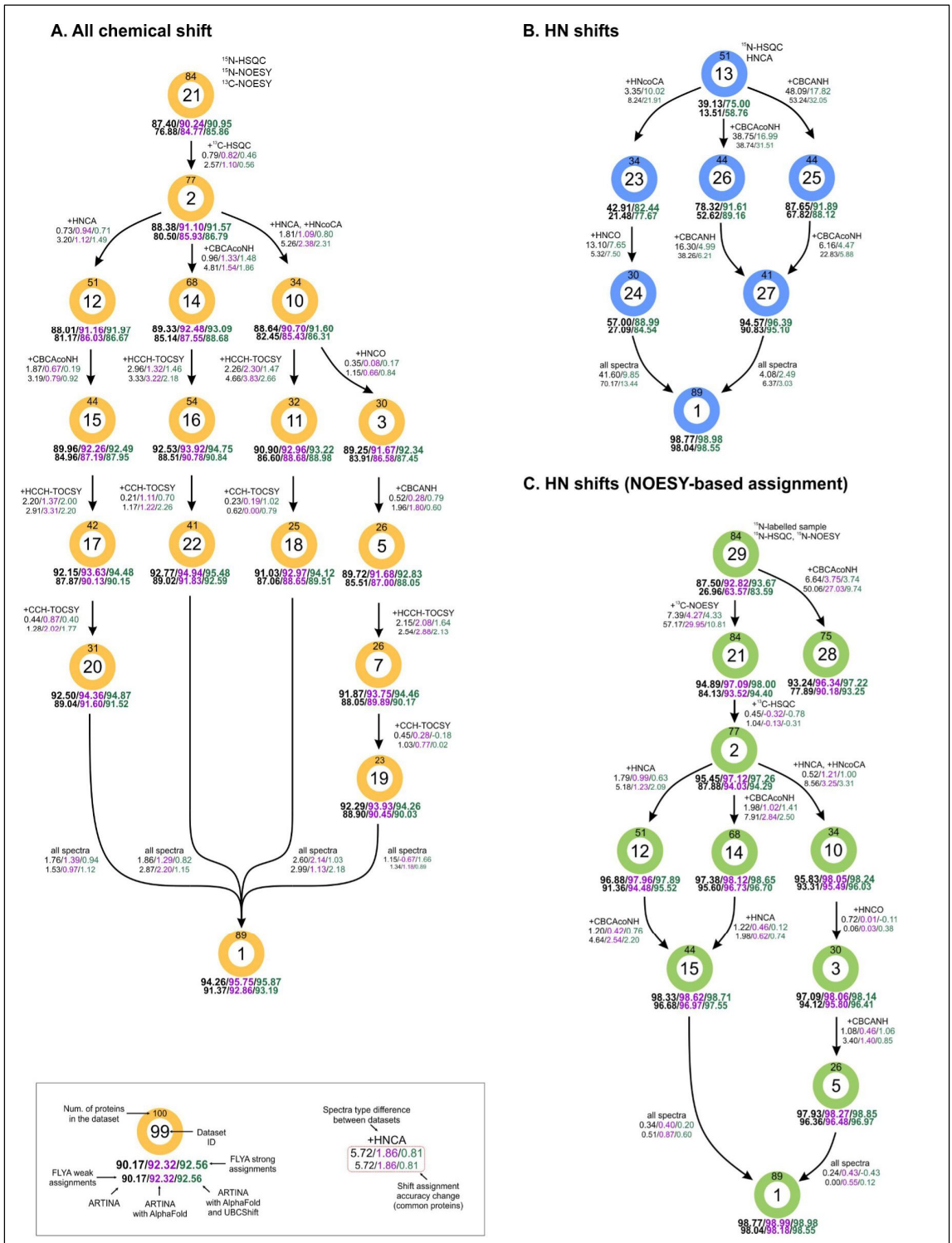

Figure 2. Impact of the spectra subset selection on the accuracy of chemical shift assignment with ARTINA with and without use of AlphaFold2 structures. Numbers below circles give the percentage of correct assignments. Selection of the optimal spectra subset (22) with complementary input from AlphaFold2 structures allows identification of the chemical shifts at higher accuracy than when all spectra are used as input but without AlphaFold2 structures.

４．研究成果

In this project, we introduced ways to enhance, in terms of accuracy and efficiency, automated protein chemical shift assignment with ARTINA by complementing the NMR spectra with other types of input data, in particular 3D structures. This allows to reduce the number of NMR spectra that are needed to establish the assignment of the protein.

Among the many possible choices of reduced sets of NMR spectra, our calculations revealed optimal sets of NMR spectra for full (backbone and sidechain) and backbone amide group assignment (Figure 2). These yield, together with input 3D structures predicted by AlphaFold2, equally or almost equally good assignments as the complete sets of (on average more than 13) experimental spectra that are available for these proteins. On this basis, we recommend the following sets of spectra for obtaining chemical shift assignments in proteins with ARTINA:

Table 1. Recommended spectra for protein chemical shift assignment with ARTINA.

Assignment task	**Recommended spectra**		**Accuracy[a] (%)**
	2D	3D	
Full (backbone & sidechains)	N15HSQC C13HSQC	N15NOESY C13NOESY CBCAcoNH HCCH-TOCSY CCH-TOCSY (Set 22)	95.5
Backbone HN groups	N15HSQC	N15NOESY C13NOESY (Set 21)	98.0
Backbone HN groups; ^{15}N-labeling only	N15HSQC	N15NOESY (Set 29)	93.7

[a] Accuracy refers to the median of the accuracy of the strong assignments obtained for the proteins in our study.

On average, five 3D spectra are sufficient to achieve more than 95% accuracy for the assignments that are classified as strong (reliable) by the algorithm. The latter comprise the large majority (92%) of all shifts. An even higher median accuracy of 98% can be achieved for the backbone amide groups using just two 3D spectra. Interestingly, backbone amide group assignment works slightly better with the NOESY spectra than with dedicated triple-resonance backbone assignment spectra. Considering that the NOESY spectra provide a wealth of other relevant information, e.g., about the conformation or multiple states of a protein, whereas the triple-resonance through-bond spectra have little use beyond establishing the assignment, this renders NMR studies more efficient in that the spectra can be used simultaneously for assignment and other purposes.

It should be noted that AlphaFold2 provides protein structures essentially “for free”, using only the sequence as input and without additional measurements, and that these structures have in general a high accuracy. This extends the range of application of structure-based assignment to most proteins. The main increase of efficiency in protein chemical shift assignment with ARTINA is the machine learning-based, complete automation of the entire process, starting from the uninterpreted spectra, which leaves the NMR measurements as the main time-limiting step. Using the small sets of spectra identified in this paper, the NMR measurements, and thus the effort and cost, for the NMR assignment of a protein can be reduced significantly, which facilitates a wide range of NMR studies of proteins.

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３．学会等名
EMBO Workshop When predictions meet experiments: the future of structure determination, Palermo, Italy（招待講演）（国際学会）

４．発表年
2022年

１．発表者名
Peter Guentert

２．発表標題
Automated biomolecular NMR spectra analysis, assignments, and structures with the deep learning technique ARTINA

３．学会等名
43rd FGMR Discussion Meeting of the German Chemical Society, Karlsruhe, Germany（招待講演）

４．発表年
2022年

１．発表者名
Peter Guentert

２．発表標題
Automated biomolecular NMR spectra analysis, assignments, and structures with the deep learning technique ARTINA

３．学会等名
Biomolecular NMR: Advanced Tools, Machine Learning. Advanced hands-on PhD course, University of Gothenburg, Sweden（招待講演）

４．発表年
2022年

〔図書〕　計0件

〔産業財産権〕

〔その他〕

NMRtist
https://nmrtist.org/

6．研究組織

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7．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

8．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関