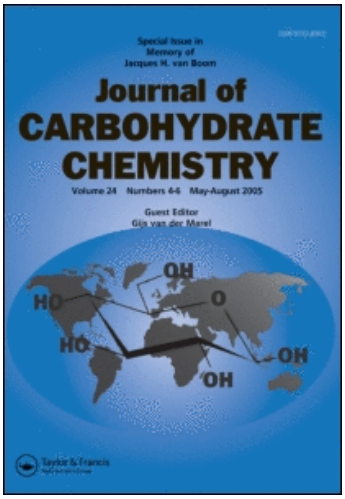

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Application of Artificial Neural Networks for Analysis of ^{13}C NMR Spectra of Fucoidans

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A new approach for structure determination of native and O-desulfated fucoidans by the analysis of their ^{13}C NMR spectra by artificial neural networks (ANNs) is described. Two ANN models were studied: the simple three-layer feed-forward network, which employs supervised learning, and the adaptive resonance theory (ART) network with unsupervised learning. Training sets for the networks were constructed using chemical shifts of synthetic oligofucosides. The results obtained demonstrate that both models worked better in the case of desulfated fucoidans, while the ART-type networks gave better results in sulfated (native) fucoidan structure elucidation.

Keywords Fucoidans; Structure elucidation; NMR spectra; Feed-forward neural network; Adaptive resonance theory

INTRODUCTION

To analyze and determine the structure from the NMR spectrum, an incremental approach has been used widely and successfully for many classes of organic

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compounds and also for carbohydrates.[1] The approach requires a database of chemical shifts and so-called increments, which in the case of polysaccharides are glycosylation and substitution effects, and sometimes corrections to these increments, so-called deviations from additivity.[2] Thus, such an algorithm can be used to model an NMR spectrum for the known structure. In the case of saccharides, it can be applied for structure elucidation with the prerequisite knowledge of the monosaccharide composition.

However, an alternative method exists to model a spectrum for a known structure. This mathematical algorithm is called the artificial neural network (ANN). The use of artificial neural networks in chemical spectroscopy was suggested by several authors. The examples include the prediction of ^{13}C chemical shifts for substituted aromatic compounds,[3] other classes of organic structures,[4] and saccharides.[5] In all the cited works a spectrum was generated for a known or supposed structure. In our work we investigate the possibility of solving the reverse problem: the direct determination of a structure from a spectrum.

Two advantages can be thought of for this approach. First, this algorithm should ideally function in the manner similar to that of a chemist analyzing a spectrum, so no assumptions about the complexity of a molecule are needed as it is deduced automatically by the presence and the number of some characteristic groups of signals. This is especially useful when dealing with spectra of highly irregular polysaccharides. The second advantage is that ANN is expected to work more rapidly than traditional incremental methods due to its massive parallelism.

Fucoidans form a class of such irregular highly sulfated polysaccharides that consist mainly of α-L-fucose with some galactose, xylose, mannose, and uronic acid as carbohydrate components. Their structural diversity is still poorly understood. Meanwhile, these biopolymers are characterized by different types of biological activity and thus are interesting objects for structural studies. Recently, a large number of oligofucosides have been synthesized in our group and their ^{13}C NMR spectra have been recorded.[6–8] We attempted to use these NMR data for the analysis of spectra of some native fucoidans along with their desulfated modifications by two artificial neural network models.

RESULTS AND DISCUSSION

General Considerations and Computational Details

Software used in this work was Stuttgart Neural Network Simulator (SNNS), v. 4.2 (© 1990–1995, IPVR, University of Stuttgart, © 1996–1998, WSI, University of Tübingen) for the feed-forward networks, and ART Gallery

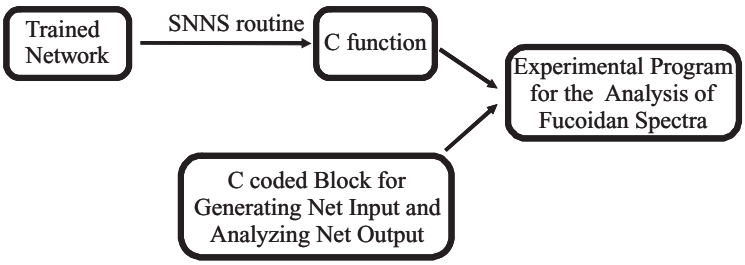


Figure 1: Algorithm used in this work.

v. 1.0 (developed by Lars Liden, URL: http://cns-web.bu.edu/pub/laliden/WWW/nnet.frame.html) for adaptive resonance theory (ART)-type networks.

The idea before this investigation was to construct an ANN that would be able to recognize various classes of fucose residues by their characteristic chemical shifts. To the best of our knowledge, only one work has been published dedicated to the analysis of fragments of ^{1}H NMR spectra.[9] Both software suites used in this work provide facilities to convert a trained network into a C-code function, which in turn could be incorporated into a homemade program. In our case, we made this function work together with routines generating possible combinations of signals from a given spectrum, presenting them in a form suitable for ANN input, then taking the ANN output and presenting it in a human readable form (Fig. 1).

Simple Feed-Forward Networks

This type of ANN is the most common and includes, among the examples of its successful employment for chemical needs, the prediction of NMR chemical shifts,[11] vapor pressures,[12] binding affinities,[13] and many others. The principal scheme of simple three-layer feed-forward ANN is shown in Figure 2.

The goal of this approach is to train ANN by the use of pairs "input → desired output" forming the training set to reproduce correct outputs for input values not presented to the network during learning. In our case, the input vectors were formed of six ^{13}C chemical shifts corresponding to a certain monofucoside residue, which gave six input neurons, each taking one chemical shift as its activation value. Output neurons corresponded to different classes of fucose residues that were found among the synthetic oligofucosides. Obviously, the activation of output neurons, a value from the range 0 to 1, could be interpreted as the probability of the input belonging to that class. It was found that different types of fucosylations for the glycosylating residue (especially O-2 vs. O-3) could not always be distinguished using feed-forward networks.

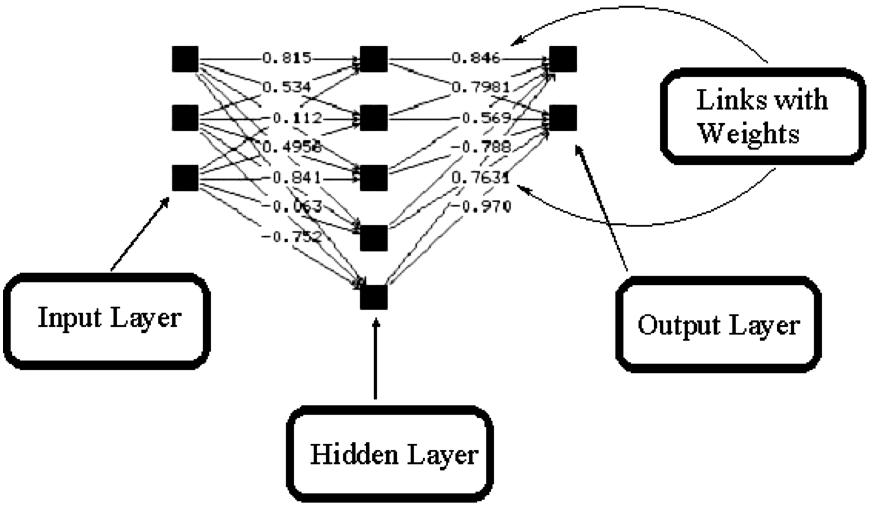


Figure 2: General structure of three-layer feed-forward neural network constructed with Stuttgardt Neural Network Simulator (SNNS).

Therefore, we had to keep the number of classes to a minimum in the case of feed-forward ANN and used 19 output neurons for 19 classes.

The number of neurons in the hidden unit for feed-forward networks is often chosen using the "trial and error" method. On the one hand, it should be large enough for the network to be capable of learning the dependence between the output and input. On the other hand, very large dimensions of the hidden layer slow down the network performance significantly. Another point to keep in mind is that besides the training set, the network also needs a so-called validation set (i.e., input-output pairs not shown to the network during training but used to test the overall error of the trained network). Training is usually stopped at the minimum of a validation error. In our case, we could not construct the validation set and thus measure the validation error directly. Instead, snapshot networks were written to disk during training and then converted to C language functions and used to test the performance of the network on the spectra of polysaccharides and higher oligofucosides, as shown in Figures 3 and 4.

It turned out that the best results could be achieved when the number of neurons in the hidden layer was set to 40. Also, several learning algorithms were tested. Among them, the resilient back-propagation function[15] was found to perform best. Software default update and initialization functions were used (topological order and weight randomization, respectively).

First, the training pattern set was created using chemical shifts of synthetic oligofucoside structures up to trisaccharides. The results obtained after the training procedure are presented in Table 1. The score column in Table 1 is

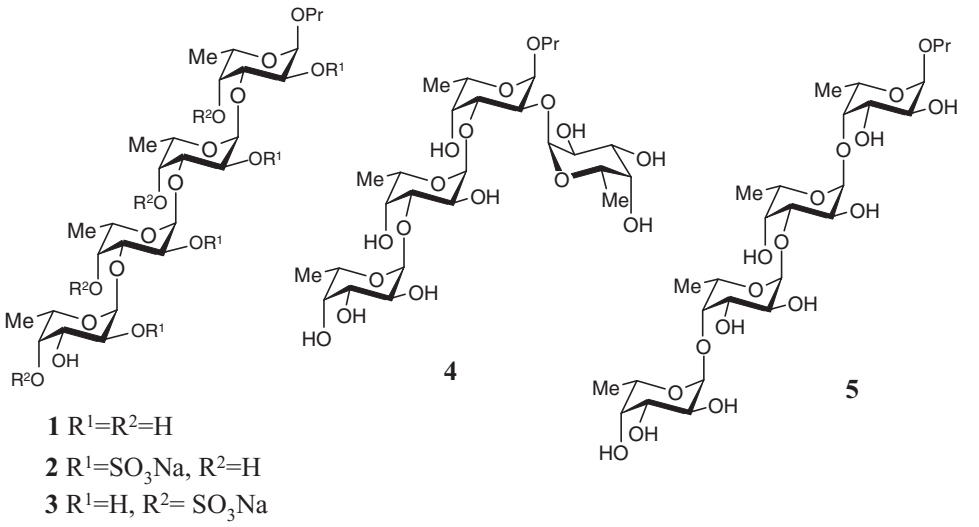


Figure 3: Tetrasaccharides used to test the feed-forward ANN behavior.

the average neuron activation for all groups of signals identified as belonging to the given class. These results are still not satisfactory. For the test oligofucosides, besides the fragments really present in the structures, some residues were identified with a high score, which did not belong to them. For example, a 2,3-branched fucose residue was found during the analysis of chemical shifts of linear tetrafucoside **1**, and in the case of sulfated tetrasaccharide **3** two false residues were found. Also, residue **Fuc-x**, nonsubstituted glycosylating fucose, was identified with a high score for nonsulfated fucoidan from *Fucus evanescens*. It can be noted that the performance of the ANN in the case

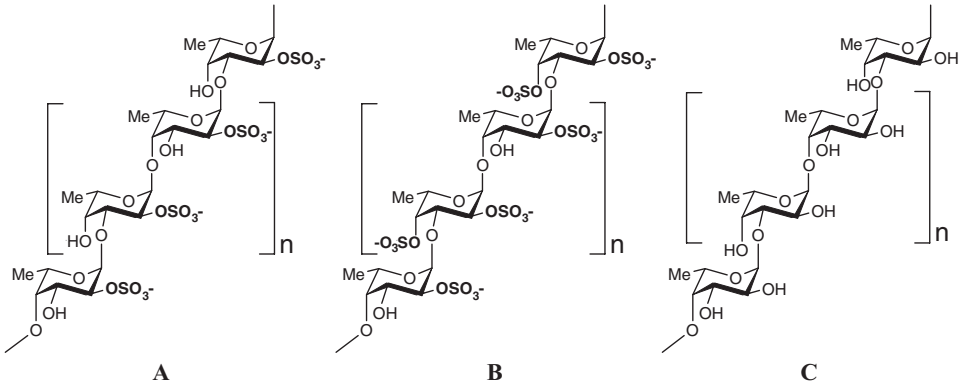


Figure 4: Structures of polymers used to test the ANN behavior. **A:** Deacetylated form of fucoidan from *F. evanescens*.[13] **B:** Deacetylated form of fucoidan from *F. distichus*.[14] **C:** Deacetylated and desulfated form of fucoidan from *Fucus evanescens*.

Table 1: Results obtained with the feed-forward network for tetrafucosides **1**–**5** and polysaccharides A–C (Fig. 4)

Compound	Found residues[a]	Score
1	Fuc(1→x	0.9214
	→2,3)FucOPr	0.9166
	→3)Fuc(1→x	0.8901
2	2-O-sulfo-(→3)Fuc(1→x	0.9127
	Fuc(1→x	0.8889
3	→2)-3,4-di-O-sulfo-Fuc(1→x	0.9162
	→3)-2,4-di-O-sulfo-Fuc(1→x	0.9149
	→3)-4-O-sulfo-Fuc(1→x	0.8986
4	Fuc(1→x	0.9437
	→2,3)Fuc(1→OPr	0.9118
	→2)Fuc(1→x	0.8892
	→3)Fuc(1→x	0.8453
5	Fuc(1→x	0.9308
	→3)Fuc(1→x	0.9009
	→4)Fuc(1→x	0.8744
A	→2,3)Fuc(→OPr	0.8808
	→4)-2-O-sulfo-Fuc(1→x	0.8344
	4-O-sulfo-Fuc(1→x	0.8228
B	→3)-2,4-di-O-sulfo-Fuc(1→x	0.8955
	→4)-2-O-sulfo-Fuc(1→x	0.8492
	→2)Fuc(1→x	0.8263
C	Fuc(1→x	0.9121
	→3)Fuc(1→x	0.8924
	→4)Fuc(1→x	0.8890

[a]All fucose units have α-L-configuration.

of nonsulfated compounds is somewhat better than in the case of the sulfated ones.

The way to correct the network recognition ability could be the inclusion of additional patterns from higher oligosaccharides and perhaps from polymers with the already determined structure into the training set. However, this attempt resulted in slowing down of the network training, while the distinguishing and recognition ability of the network did not increase significantly. It was concluded that the feed-forward network could not serve as an instrument for solving our problem: it did not distinguish between the positions of fucosylation for the glycosylating residue, and its overall capability to correctly identify signal groups appeared to be poor.

ART Networks

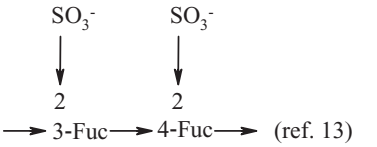
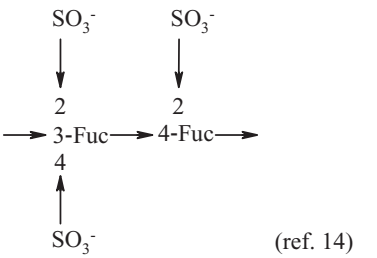
The adaptive resonance theory was first introduced by S. Grossberg in 1976.[16,17] Its primary application is for pattern classification and recognition. The ART-type ANNs have significantly more complicated topology than the feed-forward networks, and unlike the latter, they do not need output values

for their training. The goal of their learning process is to divide input patterns into several classes based on their similarity. The decision of putting a pattern into a class is made exclusively by the network; hence, this is called unsupervised learning. After the learning is finished, the network is presented by a pattern and decides to which of the already existing classes it belongs, or produces the answer "unclassified" if the pattern seems to belong to none.

ART1 is an ART-type ANN that can only deal with binary inputs (i.e., vectors containing only 0s and 1s).[18] Therefore, first we had to convert real values of chemical shifts into binary strings. As in this work we only planned to deal with fucose residues, the spectrum in a region from 15 ppm to 105 ppm was of interest to us. It yields 90 ppm range, which if accuracy of 0.1 ppm is used, can be represented as 900 points. Each point is assigned the value of 0 if no chemical shift corresponds to it, and 1 if there is one. Thus, the task of the ART1 network was to classify binary strings consisting of six 1s and 894 0s. After that, the network could be used within our homemade program for spectra analysis in a way similar to that of the feed-forward networks.

In the case of ART networks, the number of classes into which the patterns are divided plays an important role. If the network is not very strict about finding varieties between the inputs, several patterns may appear in the same

Table 2: Results of ART1 ANN testing

Fucoidan	Discovered fragments[a]	Structure determined by the combination of NMR chemical methods
De-*O*-sulfated and de-*O*-acetylated fucoidan from *F. evanescens*	→4)Fuc(1→, →3)Fuc(1→	→4)Fuc(1→3)Fuc(1→
De-*O*-acetylated fucoidan from *F. evanescens*	→4)-2-O-sulfo-Fuc(1→, →3)-2-O-sulfo-Fuc(1→	 (ref. 13)
De-*O*-acetylated fucoidan from *F. distichus*	→3)-2,4-di-O-sulfo-Fuc(1→, →4)-2-O-sulfo-Fuc(1→	 (ref. 14)

[a]All fucose units have α-L-configuration.

Table 3: Structural fragments whose ^{13}C NMR chemical shifts were applied to construct the training set for ANN

Structure code[a]	Used structural fragment[a]	Structure code	Used structural fragment[a]
-	Fuc(1→OPr	(f2s3f→3F2→f2s)	→2,3)Fuc(1→OPr
(F2f)	Fuc(1→2	(F2s3f23ff2s)	2-O-sulfo-Fuc(1→3
(F2f4s)	Fuc(1→2	(f2s3F23ff2s)	→3)Fuc(1→3
(f23Ff)	Fuc(1→2	(f2s3f-3f2-F2s)	2-O-sulfo-Fuc→2
(f4s23Ff)	Fuc(1→2	(F34ff)	→3,4)Fuc(1→OPr
(f3f23Ff) (**4**)	Fuc(1→2	(f34Ff)	Fuc(1→3
(F3f)	Fuc(1→3	(F23ff4sss)	4-O-sulfo-(→2,3)Fuc(1→OPr
(F3f4s)	Fuc(1→3	(F4s23f4sf)	→2,3)-4-O-sulfo-Fuc(1→OPr
(f23fF)	Fuc(1→3	(F4s23ff)	→2,3)-4-O-sulfo-Fuc(1→OPr
(f4s23fF)	Fuc(1→3	(f4s23f4sF)	Fuc(1→3
(F3f3f) (**1**)	Fuc(1→3	(f4s23F4sf)	4-O-sulfo-Fuc(1→2
(F3f3f3f)	Fuc(1→3	(f23Ff4sss)	4-O-sulfo-Fuc(1→2
(F3f23ff) (**4**)	Fuc(1→3	(f23fF4sss)	4-O-Fuc(1→3
(F4f)	Fuc(1→4	(f2F4s)	→2)-4-O-sulfo-Fuc(1→OPr
(f34fF)	Fuc(1→4	(f2F4ss)	2→)-4-O-sulfo-Fuc(1→OPr
(f2F)	→2)Fuc(1→OPr	(F2f4ss)	4-O-sulfo-Fuc(1→2
(f3F)	→3)Fuc(1→OPr	(F3f2ss)	2-O-sulfo-Fuc(1→3
(f3f3F) (**1**)	→3)Fuc(1→OPr	(f3F2ss)	3→)-2-O-sulfo-Fuc(1→OPr
(f3f3f3F)	→3)Fuc(1→OPr	(F3f3f2sss) (**2**)	2-O-sulfo-Fuc(1→3
(f3F3f) (**1**)	→3)Fuc(1→3	(f3F3f2sss) (**2**)	3→)-2-O-sulfo-Fuc(1→3
(f3f3F3f)	→3)Fuc(1→3	(f3f3F2sss) (**2**)	3→)-2-O-sulfo-Fuc(1→OPr
(f3F3f3f)	→3)Fuc(1→3	(f24ss3F2s)	3→)-2-O-sulfo-Fuc(1→OPr
(f4f3F4f3F4f)	→3)Fuc(1→4	(f3f-3f2-F4ssss)	4-O-sulfo-Fuc(→2
(f4F)	→4)Fuc(1→OPr	(f3f23fF4ssss)	→2,3)-4-O-sulfo-Fuc(1→OPr
(f4F3f) (**5**)	→4)Fuc(1→3	(F3f23ff4ssss)	4-O-sulfo-Fuc(1→3
(f4f3F) (**5**)	→3)Fuc(1→OPr	(f3F23ff4ssss)	3→)-4-O-sulfo-Fuc(1→3
(f4F3f4f3f4f)	→4)Fuc(1→3	(f3F4s)	3→)-4-O-sulfo-Fuc(1→OPr
(f4f3f4F3f4f)	→4)Fuc(1→3	(F3f4ss)	4-O-sulfo-Fuc(1→3
(F4f2ss)	2-O-sulfo-Fuc(1→4	(f3F4ss)	3→)-4-O-sulfo-Fuc(1→OPr
(f4F2ss)	4→)-2-O-sulfo-Fuc(1→OPr	(F3f3f4sss) (**3**)	4-O-sulfo-Fuc(1→3
(F4f3f2sss)	2-O-sulfo-Fuc(1→4	(f3F3f4sss) (**3**)	3→)-4-O-sulfo-Fuc(1→3
(f4F3f2sss)	4→)-2-O-sulfo-Fuc(1→3	(f3f3F4sss) (**3**)	3→)-4-O-sulfo-FucOPr
(f4f3F2sss)	3→)-2-O-sulfo-Fuc(1→OPr	(F24ss3f2s)	2,4-di-O-sulfo-Fuc(1→3
(f4F3f4f2ssss)	4→)-2-O-sulfo-Fuc(1→3	(F234sss)	2,3,4-tri-O-sulfo-Fuc(1→OPr
(f4f3f4F2sss)	4→)-2-O-sulfo-Fuc(1→OPr	(F234sss2f34ss)	2,3,4-tri-O-sulfo-Fuc(1→2
(f4f3F4f2ssss)	→3)-2-O-sulfo-Fuc(1→4	(f234sss2F34ss)	2→)-3,4-di-O-sulfo-Fuc(1→OPr
(F23ff)	→2,3)Fuc(1→OPr	(F234sss3f24ss)	2,3,4-tri-O-sulfo-Fuc(1→3
(f3f→3F2←f)	→2,3)Fuc(1→OPr	(f234sss3F24ss)	3→)-2,4-di-O-sulfo-Fuc(1→OPr
(f3F23ff) (**4**)	→3)Fuc(1→3	(f4s3F24ss)	3→)-2,4-di-O-sulfo-Fuc(1→OPr
		(F4s3f24ss)	4-O-sulfo-Fuc(1→3

[a]Structural code explanation: Letter "f" denotes fucose residue, and "s" denotes O-sulfo group; numbers stand to denote the position of either fucosylation and/or sulfation. Capital "F" denotes the residue in the given structure, whose chemical shifts values were used as a part of the training set. All fucose units have α-L-configuration.

class when, in fact, they should be in different ones. Actually, the network can be instructed to always put each pattern into its own unique class, but this would mean that after the training each new pattern would be reported as unclassified (i.e., the network would not be able to recognize anything except

what it had learned during the training). This aspect of ART networks' behavior is controlled by the parameter called vigilance, which is a real number lying in the range between 0 and 1. It was found after some experiments that the value of 0.55 suits our situation. However, even then, many patterns got into unique classes. Lowering the value of vigilance led to putting actually different patterns into the same classes, so it was decided to continue experiments with the ANN under these conditions.

Initially only chemical shifts of synthetic compounds up to trisaccharides were used as in the case of the feed-forward network. Testing the network trained with the above vigilance showed that some higher oligosaccharides and desulfated fucoidan from *Fucus evanescens*, as well as all sulfated fucoidans, were poorly recognized. It is in correlation with the fact that the approximation of the NMR spectrum of polymers with that of di- and even trisaccharides may be rather coarse.[19] However, with the use of the ART1 network, we could afford adding chemical shifts from higher oligofucosides without the loss of performance. After this was done, the validation was repeated with better results, which are presented in Table 2. The resulting training set is presented in Table 3.

As can be seen from Table 2, employing the ART-type network, we were able to correctly determine all the fragments found in the test polysaccharides. This suggests that the work is continued using the ART network with the inclusion of additional data into the training set.

CONCLUSIONS

Neural network analysis of ^{13}C spectra of carbohydrates was explored. Two types of ANNs were used, namely, three-layer back propagation ANN and ART1-type ANN. It was shown that the back-propagation ANN gave unsatisfactory results when validated using real spectra of natural polysaccharides. This failure is attributed to the very "general" nature of this type of ANN. On the contrary, ART1-style networks seemed to work better. Spectra of three polysaccharides both in natural forms and with sulfo groups removed were successfully analyzed, which confirms that such an approach can be used for the analysis of polysaccharides. However, ART1 networks seem to be very sensitive to the scope of the training set. It is required that exactly the residues found in polymers are included in the training set. Further work proceeds in obtaining data for the residues that are now absent.

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