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Artificial neural network prediction of quantitative structure - retention relationships of polycyclic aromatic hydrocarbons in gas chromatography

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Abstract: A feed-forward artificial neural network (ANN) model was used to link molecular structures (boiling points, connectivity indices and molecular weights) and retention indices of polycyclic aromatic hydrocarbons (PAHs) in linear temperature-programmed gas chromatography. A randomly taken subset of PAH retention data reported by Lee *et al.* [*Anal. Chem.* **51** (1979) 768], containing retention index data for 30 PAHs, was used to make the ANN model. The prediction ability of the trained ANN was tested on unseen data for 18 PAHs from the same article, as well as on the retention data for 7 PAHs experimentally obtained in this work. In addition, two different data sets with known retention indices taken from the literature were analyzed by the same ANN model. It has been shown that the relative accuracy as the degree of agreement between the measured and the predicted retention indices in all testing sets, for most of the studied PAHs, were within the experimental error margins ($\pm 3\%$).

Keywords: retention index, GC, ANN, PAHs, QSRR, molecular descriptors.

INTRODUCTION

Since some of polycyclic aromatic hydrocarbons (PAHs) are known to be carcinogenic and/or mutagenic to human beings, increasing importance is being given to their presence in the environment.^{1,2} Moreover, the measurement of the content of these micropollutants in environmental materials is mandated by most regulatory agencies worldwide.

As each PAH has a different toxicity, it is highly recommended to measure the concentration of individual PAHs. The very large number of PAHs to be quantified demands the employment of powerful separation techniques, such as gas chromatography (GC) or high-performance liquid chromatography (HPLC).³ Progra-

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mmed-temperature GC has commonly been used to separate a mixture of 16 priority pollutant PAHs. However, when more PAHs are to be measured, the GC separation becomes very difficult. Owing to very similar physicochemical properties of some PAHs, overlapping of their GC peaks frequently occurs. In order to optimize the GC separation of PAHs, the retention behavior of each PAH has to be investigated. The effect of a linear temperature ramp in GC, as the most important variable, on the retention times of PAHs can be described by a quadratic equation.⁴ An artificial neural network (ANN) may be applied to predict the retention times of PAHs when there is more than one variable.⁵

Instead of studying the retention times, the retention index (I) concept, as a very useful tool for the presentation and interpretation of chromatographic data, has been widely used in GC.⁶ In linear temperature-programmed GC of PAHs, the most commonly used approach to retention index studies proposed by Kovats⁷ is not applicable. Lee *et al.*⁸ presented a relationship employed for the generation of the retention indices of 209 PAHs. The PAH retention indices were calculated using naphthalene, phenanthrene, chrysene, and picene as internal standards according to Eq. (1):

$$I = 100 \frac{T_{R(\text{substance})} - T_{R(C_z)}}{T_{R(C_{z+1})} - T_{R(C_z)}} + 100 \cdot z \quad (1)$$

where $T_{R(\text{substance})}$ is the retention time of the substance for which the retention index is to be determined, $T_{R(C_z)}$ and $T_{R(C_{z+1})}$ are defined as retention times for PAH internal standards, which embrace the substance of interest, and z is the number of rings in the PAH standard that elutes prior to the substance of interest.

A quantitative structure – retention relationship (QSRR) relating a quantitative measure of the chemical structure to the retention behavior⁹ has been demonstrated to be a powerful tool for the investigation of chromatographic parameters. QSRRs are most often expressed in the form of a linear equation the independent variables of which are molecular descriptors and the dependent variable of which is a retention index. There is a large number of published articles dealing with QSRRs in GC. QSRRs have been used to obtain simple models to explain and predict the chromatographic behavior of alkanes,^{10,11} alkenes,¹² esters, alcohols, aldehydes and ketones,^{13–16} alkylbenzenes,^{17–21} polychlorinated naphthalenes,²² terpenes,²³ flavonoids,²⁴ hydrocarbons of naphthas,²⁵ α -, β_1 -, and β_2 -agonists,²⁶ O-, N-, and S- heterocyclic compounds,²⁷ polybrominated diphenyl ether congeners,²⁸ methyl-branched hydrocarbons produced by insects,²⁹ and a vast number of diverse organic compounds with highly diverse chemical structures.^{9,30–33} A few QSRR studies dealt with the prediction of chromatographic retention data of PAHs from their structure.^{34–38}

The importance of molecular descriptors of PAHs (quasi-length of the carbon chain and pseudo-conjugated system surface area,³⁶ molecular mass,³⁷ and connectivity index) on the nonpolar GC phase³⁸ and several thermodynamic, electronic,

steric and topological descriptors (HOMO and LUMO energies and the gap between them, molecular hardness, polarizability, atomic charges, connectivity index, volume and surface area among others) in the HPLC of PAHs³⁹ were emphasized.

Recently, ANNs have become an important modeling technique in the field of QSRR studies in GC. The ANN-QSRR approach was used to study the retention behavior of alkylbenzenes,¹⁹ noncyclic and monocyclic terpenes,²³ alkanes, alkenes, alcohols, esters, ketones and ethers,^{40,41} disulfides.⁴² The advantage of ANNs lies in their inherent ability to incorporate nonlinear and cross-product terms into the model. In addition, they do not require prior knowledge of the mathematical function. The theory behind ANNs and their use in chromatography have been reported elsewhere.^{14,19,43–45}

In this study, the relationship between the GC retention index data of PAHs on an SE-52 capillary column and three molecular descriptors, boiling points, molecular masses and connectivity indices, was used to make the ANN model, which was further employed to predict the retention behavior of PAHs on different stationary phases and with different temperature programs.

EXPERIMENTAL

The measurements were performed using a Spectra-physics model SP7100 gas chromatograph with a flame ionization detector (FID). Commercially supplied PAH standards from Macharey–Nagel were used to prepare 1.0 ppm PAH solution in toluene. A 1.0 μ L aliquot was injected into an Ultra[®]-1 (cross-linked methyl silicone) capillary column (50 m x 0.32 mm, 0.5 μ m df). As the final column temperature, 290 °C was selected, while the initial temperature and the linear temperature ramp varied in the range 40 – 100 °C and 3 – 15 °C/min, respectively. The FID was operated at 330 °C and the carrier gas (N₂) flow rate was 2.0 mL/min.

The retention time for each PAH was measured in duplicate using 13 initial temperature and temperature ramp combinations. The retention indices were calculated using Eq. (1). This data set was unseen to the ANN model and was used as the ANN testing set (Test_4) to investigate if variation of the initial temperature and temperature run has an influence on the modeling.

Two different retention data sets from Ref.⁸ were used to train (Train_1) and test (Test_1) the ANN. In addition, the data from Ref.⁴⁶ (Lundstedt *et al.*) and Ref.⁴⁷ (Takada *et al.*) were also used to test the ANN (Test_2, Test_3, respectively). Details on the experimental setup used to generate these GC data are given in the cited articles.

The ANN system were simulated using the QwikNet ANN simulator (Craig Jensen, Redmond, USA).

TABLE I. ANN training data set (data set taken from ref.⁴⁸, original retention indices from ref.⁸). *Bp* – boiling point, *CI* – connectivity index, *M* – molecular weight, *I* – retention index

PAH	<i>Bp</i> /°C	<i>CI</i>	<i>M</i>	<i>I</i>
2-Methylnaphthalene	241	3.815	142.2	218.1
1-Methylnaphthalene	245	3.821	142.2	221.0
2,6-Dimethylnaphthalene	262	4.226	156.2	237.6
1,6-Dimethylnaphthalene	266	4.232	156.2	240.7
2,3-Dimethylnaphthalene	268	4.232	156.2	243.6
1,5-Dimethylnaphthalene	269	4.238	156.2	245.0

TABLE I. Continued.

PAH	<i>Bp</i> /°C	<i>CI</i>	<i>M</i>	<i>I</i>
1,2-Dimethylnaphthalene	271	4.238	156.2	246.5
Acenaphthene	279	4.445	154.2	251.3
Fluorene	294	4.612	166.2	268.2
1-Methylfluorene	318	5.028	180.3	289.0
Anthracene	340	4.809	178.2	301.7
3-Methylphenanthrene	352	5.226	192.3	319.5
2-Methylphenanthrene	355	5.226	192.3	320.2
1-Methylanthracene	363	5.226	192.3	323.3
3,6-Dimethylphenanthrene	363	5.637	206.3	337.8
Fluoranthene	383	5.565	202.3	344.0
Pyrene	393	5.559	202.3	351.2
Benzo[<i>a</i>]fluorene	407	6.022	216.3	366.7
Benzo[<i>b</i>]fluorene	402	6.017	216.3	369.4
2-Methylpyrene	410	5.970	216.3	370.2
1-Methylpyrene	410	5.976	216.3	373.6
Benzo[<i>ghi</i>]fluoranthene	432	6.309	226.3	389.6
Benzo[<i>a</i>]fluoranthene	435	6.220	228.3	398.5
Benzo[<i>j</i>]fluoranthene	480	6.976	252.3	440.9
Benzo[<i>k</i>]fluoranthene	481	6.970	252.3	442.6
Benzo[<i>a</i>]pyrene	496	6.970	252.3	453.4
Pentacene	529	7.619	278.4	486.8
Dibenz[<i>a,c</i>]anthracene	535	7.637	278.4	495.0
Benzo[<i>b</i>]chrysene	541	7.631	278.4	497.7
Anthanthrene	547	7.714	276.3	503.9

RESULTS AND DISCUSSION

To obtain a QSRR model, the compounds must be represented by molecular descriptors retaining as much structural information as possible. Here, three molecular descriptors, boiling point, connectivity index and molecular weight, were used because they had been found to have a great influence on the retention behavior of PAHs in GC (Table I).⁴⁸

A back-propagation ANN with delta-bar-delta learning algorithm was used in this study to predict the retention indices of PAHs. More details of the applied ANN algorithm and training method are available elsewhere.⁴⁴ The topological structure of the employed ANN consists of three layers: an input layer with three nodes (boiling points, connectivity indices and molecular weights), an output layer with one node (PAH retention indices), and a hidden layer, the number of nodes of which was to be optimized. To find the best ANN parameters, a trial and error approach was used. The root mean square error (*RMSE*) function was employed to

evaluate the performances of the ANN. It was computed using the following formula:

$$RMSE = \left(\left(\sum_{i=1}^n (o_i - d_i)^2 \right) / n \right)^{1/2} \quad (2)$$

where d_i is the desired output, o_i the actual output, and n the number of retention index data.

In order to determine the optimal number of hidden layer nodes, ANNs with different numbers of hidden nodes were trained. The number of hidden nodes was varied from 2 to 12. During the training, a subset of 10 % of the training set was taken as the cross-validation set in order to enable a better generalization in the ANN learning. A curve of the average RMSE versus the number of hidden layer nodes was drawn (Fig. 1). The optimum number of hidden layer nodes was found to be 5.

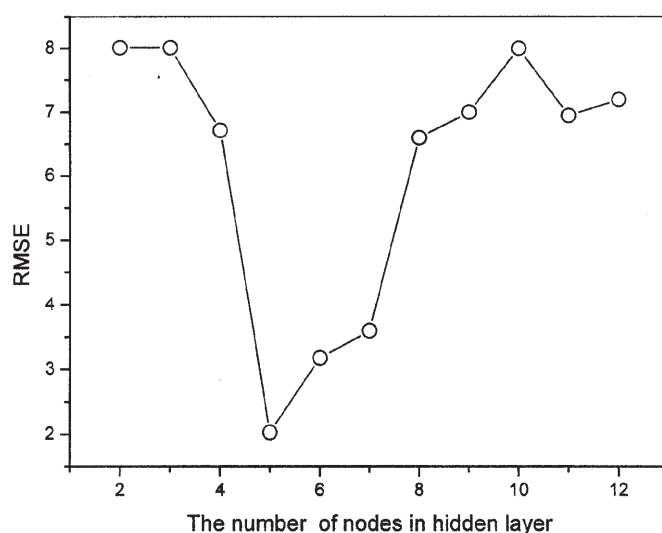


Fig. 1. Root mean square error vs. hidden node number.

To illustrate the learning process, the *RMSE* of the training and cross-validation set *versus* the learning epochs, when the number of hidden layer nodes was 5, are shown in Fig. 2. The minimum average *RMSE* value for the training and cross-validation set, for 1000 epochs, is 2.03 and 13.7, respectively. As increasing the number of epochs above 1000 led to no further significant improvements in the *RMSE*, the number of learning epochs was set at 1000.

The ANN optimized through the process discussed above was used for the prediction of the retention indices of four different testing sets (see Experimental section). The prediction results of 18 (Test_1) + 34 (Test_2) + 19 (Test_3) + 7 (Test_4) = 78 retention indices are summarized in Tables II and III. Table III presents the retention index data for the 7 PAHs experimentally obtained in this work,

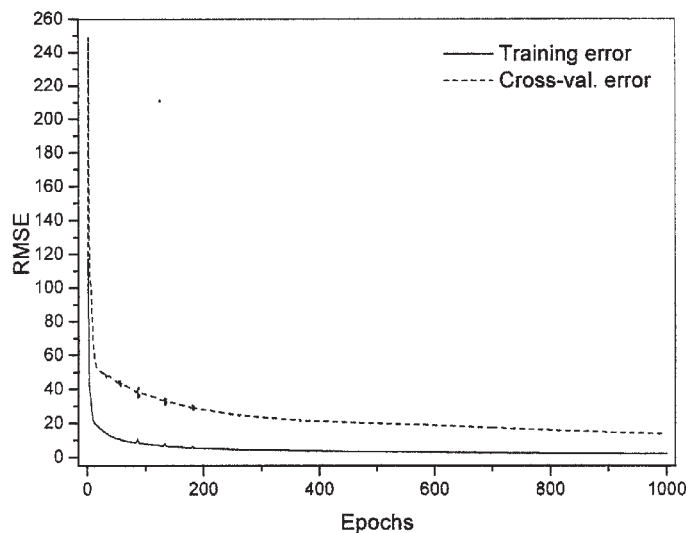


Fig. 2. Root mean square error vs. training epochs.

with different temperature programs. A total of 13 different GC runs were carried out and the retention index for each PAH was calculated. Generally, the results show that the predicted retention indices of all testing sets were in good agreement with those of the experimental data.

Table II. ANN predicted and measured GC retention indices (mean) of PAHs (data for different temperature programs)

PAH	Test_1		Test_2		Test_3	
	$I_{\text{pred.}}$	$I_{\text{exp.}}$	$I_{\text{pred.}}$	$I_{\text{exp.}}$	$I_{\text{pred.}}$	$I_{\text{exp.}}$
2-Ethyl-naphthalene	240.7	236.1	–	–	–	–
1-Ethyl-naphthalene	243.0	236.6	–	–	–	–
2,7-Dimethyl-naphthalene	239.6	237.7	–	–	–	–
1,3-Dimethyl-naphthalene	240.9	240.3	–	–	–	–
1,7-Dimethyl-naphthalene	240.1	240.7	–	–	–	–
1,4-Dimethyl-naphthalene	242.3	243.6	–	–	–	–
Acenaphthylene	239.7	244.6	239.7	247.4	–	–
2-Methylfluorene	292.2	288.2	292.2	287.7	–	–
2-Methylanthracene	323.4	321.6	323.4	320.9	–	–
9-Methylphenanthrene	321.1	323.1	–	–	321.1	319.2
1-Methylphenanthrene	323.3	323.9	323.3	323.6	323.3	320.0
4-Methylpyrene	371.2	369.5	–	–	–	–
Benzo[<i>b</i>]fluoranthene	444.5	441.7	444.5	442.1	444.5	442.7
Benzo[<i>e</i>]pyrene	449.9	450.7	449.9	451.8	449.9	452.7
Perylene	451.7	456.2	451.7	456.3	451.7	457.5
Dibenz[<i>a,h</i>]anthracene	483.3	495.5	483.3	494.5	483.3	499.0

TABLE II. Continued.

PAH	Test_1		Test_2		Test_3	
	$I_{\text{pred.}}$	$I_{\text{exp.}}$	$I_{\text{pred.}}$	$I_{\text{exp.}}$	$I_{\text{pred.}}$	$I_{\text{exp.}}$
Benzo[ghi]perylene	483.8	501.3	483.8	502.9	483.8	501.3
4H-Cyclopenta[def]phenanthrene	321.0	322.1	321.0	322.3	–	–
2-Methylnaphthalene	–	–	224.3	220.1	–	–
1-Methylnaphthalene	–	–	225.1	223.1	–	–
Biphenyl	–	–	234.0	235.0	–	–
2,6-Dimethylnaphthalene	–	–	239.6	239.7	–	–
Acenaphthene	–	–	249.9	253.3	–	–
Fluorene	–	–	266.8	269.6	–	–
1-Methylfluorene	–	–	292.3	288.7	–	–
Anthracene	–	–	301.4	301.4	301.4	301.2
1-Phenylnaphthalene	–	–	319.1	312.6	–	–
3-Methylphenanthrene	–	–	319.5	318.6	319.5	315.6
2-Methylphenanthrene	–	–	321.1	319.5	321.1	316.4
2-Phenylnaphthalene	–	–	333.5	330.5	333.5	326.5
Fluoranthene	–	–	344.3	344.9	344.3	340.1
Pyrene	–	–	350.3	352.8	350.3	348.1
Benzo[a]fluorene	–	–	368.8	366.5	–	–
Benzo[b]fluoranthene	–	–	365.7	368.9	–	–
1-Methylpyrene	–	–	371.2	374.2	371.2	370.0
Benzo[ghi]fluoranthene	–	–	392.2	390.9	392.2	389.6
Benz[a]anthracene	–	–	397.3	398.6	397.3	398.4
Benzo[k]fluoranthene	–	–	444.5	442.8	444.5	443.6
Benzo[a]pyrene	–	–	451.2	453.4	451.2	454.3
Dibenz[a,j]anthracene	–	–	482.6	489.8	–	–
Benzo[b]chrysene	–	–	484.3	498.5	–	–
Anthanthrene	–	–	484.5	508.4	–	–
Dibenz[a,c]anthracene	–	–	–	–	483.3	495.1

Table III. ANN predicted (A) and measured (B) GC retention indices (min) of PAHs (data for different temperature programs)

PAH	$I_{\text{pred.}}$	$I_{\text{exp.}}^*$	SD ^{**} _{exp.}
Acenaphthylene	249.9	247.7	1.0
Acenaphthene	249.9	253.5	0.9
Fluorene	266.8	269.4	1.0
Anthracene	301.4	301.5	0.2
Fluoranthene	344.3	338.5	4.6
Pyrene	350.3	346.0	4.6
Benz[a]anthracene	397.3	398.3	0.6

* mean value obtained from 13 measurements; ** standard deviation calculated from 13 measurements

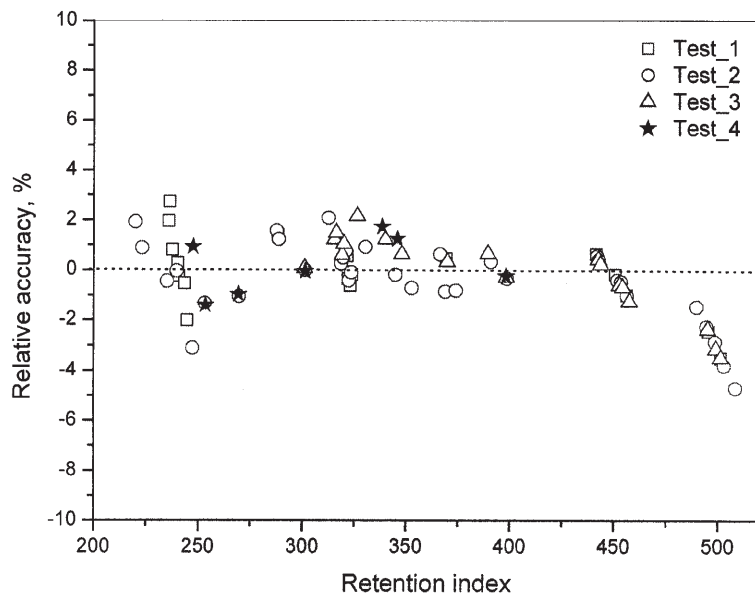


Fig. 3. Relative accuracy vs. retention index

The accuracy as the degree of agreement between the measured and the predicted retention indices for each PAH is expressed quantitatively by the relative error. The relative accuracy for all the studied PAHs shown in Tables II and III was calculated as:

$$\text{Relative accuracy} = (I_{\text{pred}} - I_{\text{exp}}) / I_{\text{exp}} \quad (3)$$

Fig. 3. shows that the maximum relative error for most of the studied PAHs is no more than 3 %. A slight underestimation is observed for the RIs of a few late-eluting PAHs.

CONCLUSION

The data used in this paper include 78 GC retention indices of 43 PAHs on different stationary phases and for different temperature programs. The results of this study demonstrate that the QSRR method in conjunction with the ANN technique can generate a suitable model for the prediction of the retention index values of PAHs. Molecular descriptors appearing in the ANN model, such as boiling points, connectivity indices and molecular weights, give sufficient information on the retention behavior in linear temperature-programmed GC. In general, for most of the studied PAHs, the relative error of the prediction is within the experimental error margins (< 3 %). For late-eluting PAHs, the prediction is somewhat worse but still satisfactory (< 5 %).

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ИЗВОД

ANN ПРЕДВИЂАЊЕ QSRR-а У ГАСНОЈ ХРОМАТОГРАФИЈИ
ПОЛИЦИКЛИЧНИХ АРОМАТИЧНИХ УГЉОВОДОНИКАСНЕЖАНА СРЕМАЦ¹, БИЉАНА ШКРБИЋ² И АНТОНИЈЕ ОЊИА¹¹Институт за нуклеарне науке "Винча", б. бр. 522, 11001 Београд, ²Технолошки факултет, Булевар Цара
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У раду је коришћен модел вештачких неуронских мрежа ANN ради повезивања карактеристика структуре молекула: тачке кључања, индекса конективитета и молекулске масе са ретенционим индексима полицикличних ароматичних угљоводоника РАН-ова) у линеарној температурно-програмираној гасној хроматографији. ANN модел је добијен несумичним узимањем ретенционих индекса за 30 РАН-ова, које је објавили Lee и сар. [*Anal. Chem.* **51** (1979) 768]. Изучавани модел је испитан са ретенционим подацима 18 РАН-ова из истог рада, као и са ретенционим индексима 7 РАН-ова експериментално добијених у овом раду. Такође, два различита скупа података са познатим ретенционим индексима су узета из литературе и анализирана помоћу истог ANN модела. Показано је добро слагање између измерених и предвиђених ретенционих индекса за све испитиване сетове података, при чему је оно за највећи број анализираних РАН-ова, у оквиру експерименталне грешке од $\pm 3\%$.

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