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USE OF MODERN COMPUTATIONAL METHODS AND NEURAL NETWORKS TO OPTIMIZE THE METHOD FOR LC/MS/MS ANALYSIS OF MILITARILY RELEVANT ORGANOPHOSPHORUS COMPOUNDS

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The search for the optimal instrumental settings of conditions in chemical analysis is typically a lengthy process. This article proposes the use of neural networks for this purpose, particularly in relation to determining the optimal conditions for the analysis of substances under study using LC/MS/MS and ESI technologies, based on the knowledge of their fundamental properties, referred to as universal descriptors. The work focuses on finding such analysis conditions that maximize the precursor ion signal. The paper specifically addresses the question of whether the results obtained from one type of analyte can be used for neural-interpolated prediction of optimal conditions for similar analytes.

Keywords: LC/MS/MS, neural networks, electron density functional theory, novichok, organophosphates, quantum chemistry, optimization

Author's statement

The department holds license No.7/2012 for the handling of highly hazardous substances granted by decision No. SÚJB/OKZCHZ/27362/2012 according to §8 and 13 of Act No. 19/1997, SÚJB/OKZCHBZ/25919/2014, and SÚJB/OKZCHBZ/7593/2020. During the experimental work, the substances covered by this license were disposed of under the internal regulations and following Act No. 258/2000 on the protection of public health.

Introduction

The nerve agents, organophosphates, are some of the most toxic synthetically derived chemical compounds known to mankind. Their primary action is to deactivate acetylcholinesterase (AChE), a key enzyme responsible for maintaining a functional concentration of the neurotransmitter acetylcholine in the postsynaptic neuronal gap[1,2]. The speed of action of these agents and their lethal effectiveness against warm-blooded organisms has led state and non-state actors to develop them with the aim of exploiting these properties against humans.

Temporal and geopolitical developments on the battlefield have led to considerations as to whether the nerve agents referred to as G-series [tabun (GA), sarin (GB), soman (GD), cyclosarin (GF)] or V-series (VX, VR, CVX) can inevitably be used only as combat agents, or whether their potential modification can yield compounds better suited to be used for subversive purposes, for the elimination of persons of high interest[3].

This shift can be traced historically to the present, with the combat use of Agent GB demonstrated in the Syrian Civil War in 2013 (ref.[4]) and 2017 (ref.[5]), but also to the targeted elimination of DPRK leader Kim Jong-un's half-brother using the more suitable Agent VX, directly at the Kuala Lumpur airport in early 2017 (ref.[6]).

These events have led to the confirmation that the substances in question are still a threat to the international community and have triggered the tightening of the control mechanisms defined by the OPCW (ref.[7]). Subsequently, substances were also added to the list of substances subject to strict control so-called A-series, known as novichok, precisely based on their use in the attempted liquidation of Sergei Skripal and his daughter Yulia in March 2018 in the city of Salisbury in the UK[8–10] with a statement of the need to have available identification instrumentation with a trace and ultra-trace disposition. This proved the suggestion that the nearly 50-year-old Soviet project of so-called fourth-generation agents[11], originating in the Cold War, is still active and its results used to attempt to eliminate human targets.

The latter incident thus catalyzed efforts at the investigative level to establish the origin of these substances and identify the alleged perpetrators, but also justified the need for research into protection against these threats, particularly in the areas of analysis, decontamination and research aimed at describing these substances structurally and chemically, defining their likely properties and toxicity.

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The absence of sufficient analytical data in connection with the A-series substances and the diversity in the leaked information from the top secret Soviet project led the research institutes to synthesize all their predicted structures and then to evaluate whether these substances carried the predicted properties and to what extent their analytical data were consistent with the samples obtained at Salisbury. In addition to the structures described by Hoenig[12] and Ellison[13], the most likely structure was that of Mirzyanov[14,15].

The importance of A-series agents, whether for combat or diversionary use, is thus undeniable. In order to develop effective protection against them, it is necessary to study them in detail and then streamline the process of their chemical analysis by different methods and from different matrices, preferably subsequently unifying it into a clear methodology.

Application of electron density functional theory (DFT)

The electron density functional theory is a method based on quantum chemistry mechanisms, which, based on the knowledge of the chemical structure of organic substances and the environment in which they are located, can optimize the studied molecule in terms of bond lengths, their vibrational states, bond angles, the strength of the electric potential, etc.[16–19.] Based on the computed data, one can then efficiently estimate the location and robustness of HOMO and LUMO orbitals, create a 3-D probability map of electron density, vector the dipole moment on the molecule, and make relatively accurate estimates on these quantized physicochemical quantities in various applications[20].

Carlsen[15] has used a wide range of software tools also using DFT as PASS, T.E.S.T., ACD/iLab, F.D.S.P.C, ACD/Percepta and QSAR Toolbox to calculate the probability of specific biological activity of selected compounds and based on these estimates concludes that there is a clear difference between the biological activity of V-series versus A-series compounds, and in terms of combat use their results speak against the A-series. The authors themselves, in a partial conclusion, describe the low probability of blocking cholinergic excitatory transmission by A-series agents as surprising.

In their work, Khafa *et al*.[21] graphically expressed the electron density of selected representatives of chemical warfare agents and on this basis subsequently assessed their disposition to chemical reactions according to visualizations of electrostatic charge dislocation on the molecule.

Bhakhoa *et al*.[20] used the M06-2X/6-311+G(d,p) method to quantify quantities that have enormous implications for considerations related to reactivity, stability, and reaction disposition. They refer to these quantities as reactivity descriptors. Based on the calculated energy balances on the molecule, the authors further flesh out these descriptors, claiming that they develop the idea of ionization and electron affinity properties of the molecule. They claim that these reactivity descriptors, allow an objective assessment of the overall stability of the molecules of the substances under investigation. They refer to the difference between the energies of the frontier orbitals as an indicator of stability and state that this increases as follows: VX < VR < A-234 < GB.

Authors Wang *et al*.[22] further develop the argument that the large HOMO-LUMO energy gap is correlated with the dipole moment, and in their study they discuss the correlation of the energy barrier with the dipole moment and other quantities related to the electron density mapping of the molecule.

Based on these findings, it can be concluded that nerve agents are generally strongly electrophilic and are thus willing to accept incoming electron density from nucleophilic species such as oxygen, nitrogen and sulphur, which from this perspective are the donor atoms preferentially acting as electropositive centres of nerve agents.

The DFT analysis of the molecules studied, or its outputs in the form of differently interpretable energy quantities, thus bring an interesting perspective on the evaluation of the molecule's disposition to reactions, to the evaluation of its polarity, ionization potential and electron affinity, and allows the analyst to anticipate possible complications and to seek solutions to them already in the planning part of the experiment. The controversy over the use of these modern methods for the development of new chemical warfare agents, for example, remains a question, of when it is possible to model their hypothetical properties, to investigate their disposition to reactions, and their biological activity.

LC/MS/MS analysis of highly hazardous organophosphorus compounds

In terms of the application of this knowledge in the field of LC/MS/MS analysis, considerations regarding sample preparation, the appropriate choice of the appropriate column and the appropriate combination of mobile phases and the appropriate choice of their modifiers are useful in the case of the LC part. The influence of the mentioned descriptors for the mass identification part is indisputable for the determination of the suitability of the test substance for the ESI technique and carries with it information and the choice of the intensity of the ionization voltage due to the possible unwanted fragmentation of the test molecule already in this pre-part of the MS/MS system.

The use of the LC method for the analysis of organophosphorus warfare agents without tandem with another identification method cannot be considered a used procedure. This is mainly due to the hydrolytic predispositions of these compounds, so direct analysis, moreover with great quantitative analytical ambitions, does not make much sense here. Also, the possibility of derivatization of the degradation products of this type of

sample, only by the silylating reagents used for GC/MS, is fundamentally impossible with this kind of instrumentation.

It is, however, very common to use tandem LC/MS/MS to analyze degradation products or high molecular weight adducts of organophosphorus BCHL with their affinity enzymes with advantage and high sensitivity. Oudejans[23] used LC/MS/MS to analyze the substance VX in the context of its stability in porous materials after decontamination. The OPCW and Lee[24] refer to the LC/MS/MS method as an effective tool for the forensic analysis of environmental and biomedical samples, where sensitivities in the order of 1 ng ml^{-1} and 0.1 ng ml^{-1} respectively can be successfully achieved in the identification of degradation and metabolic products when working in ion selection mode. Tsuchihashi[25] or Katagi[26] emphasize the importance of the LC/MS/MS method in the potential misuse of VX, building on their historical still not-too-distant analytical experience with the misuse of sarin in the Tokyo subway.

Bryant[27] used LC/MS/MS in his study and found that the degradation metabolic products of these compounds are much more stable than their "parents". Their quantity is thus a good measure of the intensity of an individual's intoxication.

GC/MS is a very efficient method for the analysis of organophosphates, however, it has its limitations for the analysis of their degradation products, where they cannot be determined directly and need to be suitably derivatized and therefore complicated to convert the degradation products into organic solvent[28–30].

Mirbabaei used Agilent 6410B triple quadrupole to study[31] the biodegradation of A-234. As a result of the study, A-234 was found to be a significant urinary marker of intoxication with this substance and the presence of adducts of A-234 with the amino acid tyrosine and the enzyme AChE was found too.

The LC/MS/MS method has thus become a relatively attractive form of determining the degradation products of chemical warfare agents using their stability, and relative polarity, which allows direct analysis of aqueous samples or aqueous extracts with little or no further treatment.

Neural networks as a tool for large-scale data processing

Attempts to transform the neural connections in the human brain into a mathematical model capable of capturing these complex nonlinearities have been known since the early 1940s. It was found that it would not be difficult to design the structure of the model, since it was only a matter of copying the analogy of the functioning of the neural network in the brain and modifying it appropriately. Thus, Donald Hebb[32] in 1949 in his groundbreaking monograph based on his study of this biological analogy and conditioned reflexes, defined an algorithm that allowed a neuron to learn by changing the weights of its inputs. He did so based on the simple idea that if a neuron is excited correctly, then the connections that led to the excitation are strengthened. Conversely, if it is excited incorrectly, then these connections must be weakened. In its early days, the method did not allow for more complex applications, as they would have required a much larger neural network topology and thus a power of computing power. The development of neural networks was also hampered by the fact that a learning algorithm for multilayer neural networks had not been defined for a long time. This was not built until 1986 on the principle of backpropagation of error. With the gradual expansion of information technology, the complexity of realistic topologies and the number of applications, including those useful in the field of chemistry[33], grew equivalently.

The classification of wines[34] addressed the hypothetical problem of whether their origin, i.e. a specific winery, can be estimated from a set of diverse chemical descriptors detectable by simple chemical analysis using a neural network. Wines, regardless of their type, were taken from three different locally related wineries and a chemical analysis of 13 characteristics was carried out (among the most important: alcohol content, malic acid, sediment content, pH of the sediment, magnesium content, phenol content, intensity of colour, etc.). Each wine thus described was assigned a winery. This dataset was used to train a neural network of ten hidden layers to discriminate, with a defined error, which wines belong to which winery.

Gasteiger[33] describes the use of neural networks in various areas of chemistry, specifically in estimating chemical reactivity, where descriptors such as total charge, dissociation energy, electronegativity, and polarity were the input to the network and the output was the expected reactivity. This model was then implemented by Röse[35] on 29 aliphatic compounds that contained 385 bonds, each of which could be further heterocyclically cleaved, creating 770 possibilities for their cleavage. After 1,300 cycles, which are referred to as epochs in neural networks, the data already showed good agreement with the expected outputs, and the network trained in this way could be used for similar types of compounds.

Tusar[36] monitored the pH and alcohol content dependencies in the HPLC analysis of the components of Spanish wines. According to the ability to separate the different characteristic components of the wine, he calculated the selectivity factor SF. Using a modelling tool published by Zupan[37] based on the method of least squares, he projected a 3-D plot onto the ground plane and interpolated the dependence of the selectivity factor (SF) on the variables already mentioned.

He then modelled the same problem using a neural network consisting of two identical input descriptors, and six neurons in one hidden layer, and the output was the observed SF. A comparison of the results of the two models can be found in Figure 1.

Otto *et al.*[38] studied the effect of the reaction conditions of benzene nitration on the formation of its monosubstituted derivative, or the ratio of the parallel

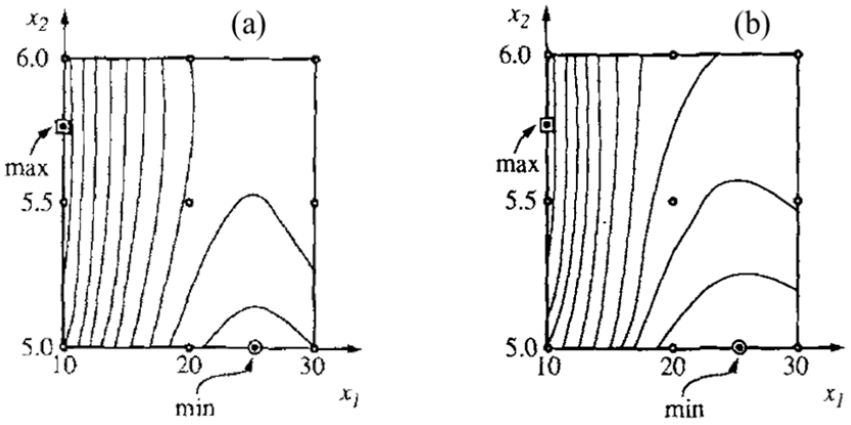


Fig. 1. **Comparison of results obtained by polynomial interpolation (a) and generated by a neural network (b)**[37]

formation of *p*-nitrobenzene and *o*-nitrobenzene and also *m*-nitrobenzene. To optimize the reaction mixture and conditions of the reaction, intending to obtain predominantly one of the derivatives, he used neural networks.

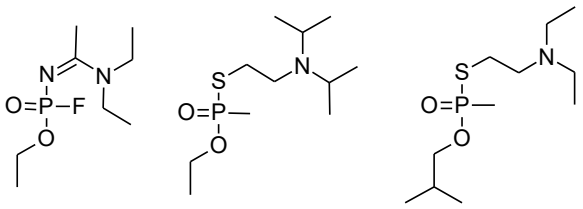
Significantly more sophisticated applications of neural networks, particularly in the field of physical chemistry, can be found, for example, in Kulichenko *et al.*[39], where the authors linked electron density functional theory with neural networks while comparing the effectiveness of these methods in an application to the calculation of the interatomic potential affecting the stability of the molecule under study. They found that the use of neural networks, or machine learning, has a noticeable effect on the number of ab initio iterations in DFT calculations, thus significantly reducing computational time and eliminating errors.

Experimental part

Based on the need to unify and accelerate the process of finding the optimal methodology for the analysis of militarily significant organophosphorus compounds by LC/MS/MS, applicable in mobile and stationary laboratories of the Czech Armed Forces, an effort was made to build on current trends in the field of neural network processing of large amounts of data and the current possibilities of DFT-based modelling of molecule descriptors.

Analytes

Ethyl *N*-[1-(diethylamino)ethyliden]phosphoramido-fluoridate (A-234, 86 %) [CAS 2387496-06-0], *S*-[2-(diiso-propylamino)ethyl]-*O*-ethyl-methylphosphonothioate (VX, 92 %) [CAS 50782-69-9], *S*-[2-(diethylamino)ethyl] *O*-(2--methylpropyl) *P*-methylfosfonothioate (R33, 73 %) [CAS 159939-87-4] (all VVÚ Brno, Czech Republic), LTQ Positive calibration solution (Thermo Scientific, USA), tributyl phosphate PHR1205 Pharmaceutical standard 99.8 % [CAS 126-73-8] (Sigma-Aldrich, USA).



A-234 VX R-33

For analysis, all analytes were prepared at a molar concentration of 40 μmol l^{-1}. Due to the low vapour tension of the analytes under investigation, weighing on a SAG 285 /M analytical balance (Mettler Toledo, Singapore) modified for weighing in a high-pressure fume hood was chosen for analytical dosing.

Solvents

Water (Optima, USA) [CAS 7732-18-5], acetonitrile (Optima, USA) [CAS 75-05-8], methanol (Biosolve) [CAS 67-56-1], formic acid (Optima, USA) [CAS 64-18-6], acetic acid (Optima, USA) [CAS 64-19-7], trifluoroacetic acid (Optima, USA) [CAS 76-05-1] all in LCMS purity.

Instrumentation

The Ultimate 3000 was used as a liquid chromatograph in a configuration consisting of consisting of a high-pressure module HPG-3200SD equipped with two side valves allowing measurements on two columns simultaneously, an automatic sample dispenser WPS-

3000TLS ANALYTICAL and a UV-VIS module DAD-3000. The columns were tempered in the TCC-3000SD module. The configuration was introduced by the SRD-3200 degasser (all Thermo Scientific, USA).

A robust LTQ XL (Thermo Scientific, USA) system with a linear ion trap and ion optics consisting of a quadrupole and an octupole was used as the mass detector in tandem with the previous instrumentation, and an ESI head was used as the ion source.

Spray gas was generated by a GENIUS XE 35 nitrogen generator (Peak, Scotland UK) with a default pressure setting of 100 psi. Compressed helium 5.0 (Linde, Czech Republic) was used as the collision gas.

Software

Chromeleon 7.2.10 [commercial license] was used to control the HPLC system and XCalibur 4.5 was used to control the LTQ XL, where intercommunication between these software modules was provided by the SII for XCalibur server interface version 1.5.0.10747 [commercial license]. Measured chromatographic data were interpreted in its QualBrowser toolbox, including the acquisition of mass spectra.

Spartan 20′ software (Wavefunction Inc., USA) [academic license] was used to generate quantum-chemical graphical outputs and calculations. Neural networks were constructed using the Deep Learning – NeuralNetwork module included in the MATLAB 2023a package (MathWorks, USA) [Campus-Wide license]. Neural network analysis scripts were also created in MATLAB to optimize the measurement conditions for selected analytes.

As a robust software to create and verify fragmentation diagrams was used Mass Frontier 8.0 SR 1, which was used for a possible interpretation of mass spectra also. (Thermo Scientific, USA) [commercial license].

Choosing descriptors for the neural network

Based on the need to optimize the ratio of the LC input parameters to the neural network output signal, the mobile phase composition (**B**), mobile phase flow rate (**Q**), and fogging gas flow rate (**E**) were chosen as "external" descriptors. However, at the same time, in an attempt to capture the influence of the physicochemical properties of the molecule, additional intramolecular "internal" descriptors were added, based on DFT analysis of the analyte. These intrinsic descriptors (Table I) also acted as a discriminating feature, allowing the neural network to assign to the values it analyzed the specific substance to which these values belonged.

MATLAB software and its Deep Learning Toolbox were used to create the neural network. A network topology (Figure 2) was designed with one input layer containing seven descriptors (B, Q, E, L, H, D, S) followed by a hidden neural layer containing a multilayer perceptron of 50 layers. The hyperbolic tangent was chosen as the activation function of the hidden layer. The output layer contained a single target, represented by the signal intensity of the precursor ion.

The neural network thus designed was trained on 396 measured data of the studied analytes such that 100 % of the data were used as training data and then the data were classified as test data (28 data from each analyte) were measured afterwards and used to verify the success of the trained network. The training was performed until the success rate of the network learning on the training data,

Table I
Variables obtained by DFT analysis

	A-234	TBF	VX
LUMO, eV (**L**)	1.77	1.9	1.61
HOMO, eV (**H**)	–10.18	–12.51	–9.12
Dipole moment, Debye (**D**)	7.77	5.39	3.92
S, J mol^{-1} K^{-1} (**S**)	478.55	549.9	540.92

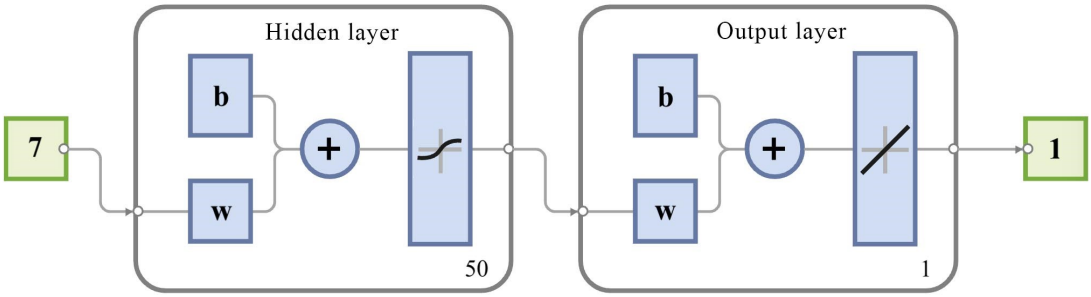


Fig. 2. Proposed topology of a neural network designed for learning from experimental data, b – bias, w – weights

and the validation of such a network on the test data, reached a value of at least 98 %. Bayesian regularization was chosen as the training algorithm.

Acquisition of experimental data

Using the XCalibur control program, the sample dispensing process was programmed to vary three essential measurement parameters, namely the mobile phase composition (B, [%]) represented by the percentage of acetonitrile, the mobile phase flow rate (Q, [µl min^{-1}]) and the ShGFR value (E, [arb]). XCalibur also instructed the periphery of the mass detector to load the appropriate file containing the tuning of the ion optics, which was optimized to TBF.

Parameter B could take values 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 [%]. The parameter Q could take values of 100, 200, 300 [µl] and the value of ShGFR was in the interval 10–40 [arb] with a step of 10 arb, i.e. it could take four values. In total, XCalibur instructed 132 possible combinations of these values to be measured for a single analyte.

For the measurements of tributyl phosphate, substance VX and substance A-235, 396 measurements were taken, which were reproduced three more times to check the stability of the monitored signal. The mobile phases were not modified in any way. A volume of 1 µl of analyte was always injected. The observed signal intensity of the precursor ion was recorded in the file.

To automate the entire process, the sample injection system was modified to ensure constant conditions for all measurements, with the minimum possible consumption of analyte and mobile phases. This was implemented by routing the sample from the autosampler away from the column and DAD, directly into the ESI. The dispensing needle was washed before and after overdosing with LCMS purity water. The measured results were recorded in a spreadsheet from where they were retrieved by the neural network and used for training.

Results and discussion

A script was programmed in the MATLAB environment to drive the trained neural network and use it to interpolate the graphical data to obtain visualizations of the experiment at a much higher resolution allowing the more accurate finding of the optimum parameters B, Q, and E. This shift in interpretation is shown in Figure 3.

By varying the variable E, with all possible combinations of the variables B and Q, its value was obtained such that the signal intensity of the precursor ion was maximized and then the optimal B_{opt} and Q_{opt} were subtracted at this value. Subsequently, an Accucore^{TM} C_{18} 2.1 mm × 150 mm × 2.6 µm column was plugged into the system, which proved to be the most suitable for eluting these groups of compounds, which were eluted isocratically according to their detected optima in the simulation of measurements using a neural network (Table II).

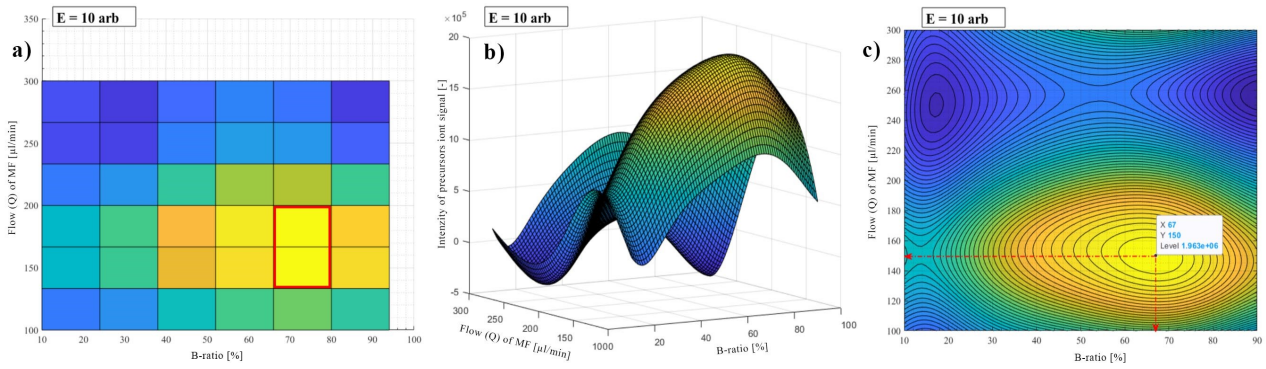


Fig. 3. **Original resolution of the measured raw data (a), projection of the neural network simulation into 3D (b), projection onto the Q, B surface (c) - all at E = 10 arb for substance A-234**

Table II
Optimal descriptor values for maximizing the signal value of the precursor ion

Descriptor	A-234	TBF	VX	R33
B-component content of mobile phase B, %	33	51	62	38
Mobile phase flow rate, µl min^{-1}	105	250	213	223
ShGFR value, arb	28.35	26.66	29.6	34.2

Table III
Numerical expression of the effect of the mobile phase modifier on the ionization of the analyte

Mobile Phase	A-234	TBF	VX	R33
Formic acid	+ 23 %	+ 15 %	+ 28 %	+ 29 %
Acetic acid	+ 36 %	+ 12 %	+ 32 %	+ 30 %
Trifluoroacetic acid	− 37 %	− 28 %	− 35 %	− 36 %

Subsequently, the collision energy was optimized to take a high-quality ms^2 spectrum of A-234 and store it in the library.

To improve the ionization of the sample, and thus obtain an even greater response to the monitored signal, the aqueous mobile phase was modified first with formic acid, then acetic acid, and finally with trifluoroacetic acid, always at a concentration of 0.1 %. The gain or loss in signal intensity can be found in Table III.

A fragmentation series analysis was performed on substance A-234 using MassFrontier software (Figure 4), with findings that find agreement with the study of other authors[24].

The possibility of the effect of hydrolysis of A-234 in contact with the mobile phase was verified with an optimum ratio of components A and B. Assuming a significant excess of mobile phase relative to the analyte, the hydrolysis observed was considered to be a first-order reaction, from which the half-life was derived 4 h 49 min and it was concluded that due to the contact of substance A-234 with the mobile phase during the elution on the column not exceeding a total time of 30 min, the effect of hydrolysis can be considered to be negligible.

In a study of the hydrolysis kinetics of A-234, it was found that optimizing a set of experiments with neural networks resulted in an overall increase in the response of the analytical system by 1,080 %. The detection limit for substance A-234 became a concentration of the order of 1 pg μl^{-1}, for substance VX 10 pg μl^{-1} and for substance R33 also 1 pg μl^{-1}, the criterion being a very generous 10:1 signal-to-noise ratio (S/N) of the ion used for quantification. The limit of quantification of such an optimized method can thus be assumed to be in the order of tens of fg μl^{-1} (S/N 5:1), which is sufficient sensitivity for the much needed determination of ultra-trace amounts of the analytes of interest.

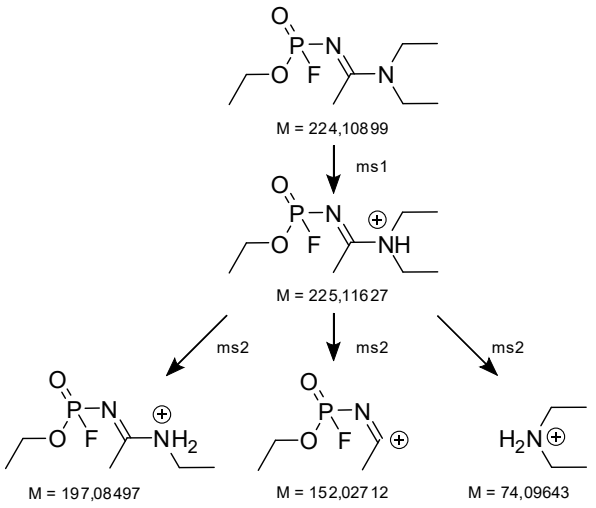


Fig. 4. **Evolution of precursor and product ions in the ms^2 spectrum of substance A-234**

Conclusion

Analytical and scientific departments are often faced with a multitude of results where the interdependence of adjustable measurement conditions and output data can be classified as a nonlinear multidimensional problem. With the expansion of computational power, the described technologies are becoming more and more accessible and applicable to different research areas. This paper is a proposal for the application of neural networks and DFT theory to the problem of optimizing the measurement conditions so that the observed output signal is as intense as possible, which in turn allows, above all, to increase the sensitivity of the identification method. This set of procedures allows to develop a measurement methodology for a given analyte, which by its sensitivity will be useful not only for the work of chemical warfare specialists, but also in other fields of scientific knowledge.

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