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Fourier and Laplace-like low-field NMR spectroscopy: The perspectives of multivariate and artificial neural networks analyses

Radu Fechete^{a,b,*}, Iris Adina Morar^{b,c}, Dumitrita Moldovan^a, Ramona Ioana Chelcea^a, Ramona Crainic^{a,b}, Simona Cornelia Nicoară^{a,d}

^a Technical University of Cluj-Napoca, 28 Memorandumului str. 400114, Cluj-Napoca, Romania

^b Babeş-Bolyai University, Faculty of Physics, Doctoral School, 1 Kogălniceanu str., 400084 Cluj-Napoca, Romania

^c IMOGEN, County Emergency Hospital, Cluj-Napoca, Romania

^d STEM Faculty, The Open University, Walton Hall, Milton Keynes MK7 6AA, UK

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ABSTRACT

Low field Nuclear Magnetic Resonance (LF-NMR) is a rich source of information for a wide range of samples types. These can be hard or soft solids, such as plastics or elastomers; bulk liquids or liquids absorbed in porous materials, and can come from biomaterials, biological tissues, archaeological artifacts, cultural heritage objects. LF-NMR instruments present a significant advance especially for *in situ*, *ex situ* and *in vivo* measurement of relaxation and diffusion. Moreover, high resolution 1D and 2D spectroscopy, as well as magnetic resonance (MR) imaging are available in these fields. In this work we discuss the advanced analysis of the data measured in LF-NMR from the perspectives of tertiary level that implies the analysis on principal components (PCA), and on the quaternary analysis that uses an artificial neural network (ANN). The principles of PCA and ANN are largely discussed. For the PCA analysis, a series of 52 spectra were analyzed, having been recorded *in vivo* by LF-NMR. Of these spectra, 38 were generated from normal uterus, 7 by uterus tissue with endometrial cancer, and another 7 were obtained from tissues of women with uterine cervical cancer. The PC1 vs PC2 plot was further analyzed using an artificial neural network, and the results are presented as 2D maps of probability. Furthermore, the perspectives of applying an ANN to solve the problem of Laplace-like inversion are discussed. An example of such ANN was presented and the performance was discussed. Finally, a model of complex ANN, capable to sequentially solve this kind of problems specific to LF-NMR is proposed and discussed.

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1. Introduction

The primary data processing usually implies the Fourier analysis or Laplace-like inversion of time domain data [1–5]. NMR is a technique that enables the measurement of multiple characteristic parameters for various types of samples, with a single instrument. This versatility is mainly based on the availability to use well designed pulse sequences. These allow an easy manipulation of pulses duration, amplitude and shape, and inter-pulses time intervals, the possibility to change the transmission and/or acquisition frequency and field gradients. Low field Nuclear Magnetic Resonance (LF-NMR), a branch of NMR technique that has initially lost some spectroscopic capabilities, is now catching up in its importance for a successful measurement. Furthermore, LF-NMR may even be the technique of choice due to the versatility of the instru-

ments, its relative low cost (for acquisition and operation), mobility of the instrument and high adaptability to the measured samples [6–8].

The samples can be in solid, liquid or gel state, and the measurement can take place in laboratory, *ex situ*, directly *in situ*, or *on-line*, for a small sample cut from a specimen, or localized for a large sample. Each material is characterized by a series of physical quantities, among which, the NMR parameters. The latter may include: the chemical shift (δ) characteristic to Fourier spectroscopy, the longitudinal and transverse relaxation times (T_1 and T_2) characteristic to NMR relaxometry, or the so called Laplace-like spectroscopy, the self-diffusion coefficient (D) characteristic to NMR diffusometry. The total of all independent parameters will characterize the state of the sample. The next step is to classify the samples according to their properties, into classes, subclasses, groups, subgroups, etc. Some fields where a simpler characterization and classification of materials can have a large impact include medical diagnostics (e.g. cancer classification), quality control in food and

* Corresponding author at: Technical University of Cluj-Napoca, 28 Memorandumului str. 400114, Cluj-Napoca, Romania.

E-mail address: rfechete@phys.utcluj.ro (R. Fechete).

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cosmetics industry, environmental monitoring, well logging, and many others.

This paper focuses on a discussion and interpretation of various levels of analysis, aiming to obtain the classification of the measured samples. The first part is a short review of LF-NMR instruments and specific samples as well as on the primary and secondary analysis of raw data. In the second part the focus is on those methods that imply multiple parameters, such as the statistics in the principal components analysis (PCA), and the method that uses an artificial neural network for a quantitative classification (ANN-QC). Although, in general, one can operate several types of analysis, in this paper we preferred to use the experimental data obtained by using LF-NMR instruments under their specific parameter settings. The principles of PCA statistical analysis and the basics of applying ANN are presented, with perspectives of using them for a largely accepted classification and analysis at a basic level. Last but not least, the authors wish to highlight the fact that as this is a special issue dedicated to Prof. B. Blümich, many of the article references are illustrating his lifework results in the area of low field NMR.

2. Summary of low field NMR

A summary of the entire process having the LF-NMR data in the center is presented in Fig. 1 [9–30]. Raw NMR data can be acquired as a one-dimensional (1D) free induction decay (FID), or as multiple-dimensional spectroscopy. The most used decay in NMR relaxometry is the decay of transverse magnetization (T_2) under the Carr–Purcell–Meiboom–Gill (CPMG) sequence [1,3,4,13–16,19,31]. The inversion recovery and saturation recovery of nuclear magnetization [1,32] are standard pulse sequences for the measurement of longitudinal magnetization, T_1 . LF-NMR relaxometry experiments have benefited from smart optimized procedures and algorithms [33–36]. For a long time, in the early stages of NMR, this was known as time-domain NMR. By fitting the relaxation and diffusion decays, and the build-up curves with model functions, specific parameters such as relaxation times and self-diffusion coefficients can be extracted [26].

The relaxometry data can be analyzed by applying a Laplace-like inverse transform to a multi-exponential decay. Here we have to mention that the ordinary used term is *Laplace inverse transform*. This would be mathematically correct for a result presented in terms of relaxation rates ($R_1 = 1/T_1$ or $R_2 = 1/T_2$). Therefore, when the result is presented in terms of longitudinal or transverse relaxation times (T_1 or T_2) we are going to use the term of *Laplace-like inverse transform*, and the T_1 - or T_2 -distributions will be named *Laplace-like spectra*.

There are multiple algorithms, such as UPEN (Uniform-penalty inversion of multiexponential decay data) [37] or CONTIN. Over the many studies that we performed, we found some reliable algorithms, able to perform one-dimensional and two-dimensional Laplace-like inversions [38]. Various types of two-dimensional Fourier-Fourier, Fourier-Laplace or Laplace-Laplace methods involving NMR relaxation and diffusion processes were magnificently developed and described by Prof. Paul T. Callaghan [39]. Laplace-like inversion algorithms are commonly based on Tikhonov regularization [40], Monte-Carlo inversions [41] or methods that include the maximum entropy [42].

For material scientists, biologists, or medical doctors to have access to a parameter map of the material/biomaterial of interest represents source of comprehensive information [16]. Such a parameter map assumes that the image is encoded with a single parameter, such as the ^1H residual dipolar couplings in Achilles tendon [43], the ^1H residual second van Vleck moment, M_2 and the corresponding correlation time [44], or proton relaxation times

T_2 and T_1 , and spin density $\rho_{1\text{H}}$ [16]. In many studies, the conclusions of investigations are presented at this point in the analysis. Nevertheless, for complex studies, that imply more than two categories (classes) of samples, the investigations can continue with a new level of data processing and interpretation.

Multivariate analysis, in particular statistical analysis by looking at the principal components (PCA), is a robust method that usually deals with many types of parameters [45–47]. It makes sense to apply PCA if the study is complex and the samples can be classified at least in two (usually several) groups [46–48]. More details about the principles of PCA analysis and a practical example will be discussed in the next section while the [Section 1 of Supplementary Materials](#) provides a full mathematical description.

The analysis can continue and the groups obtained from the PCA analysis can represent the input data into an artificial neural network (ANN). This numerical tool is a modern instrument that can perform various types of analysis (the most common ones are classification and regression) in case there is no known mathematical relationship between the input data and the desired output. To be able to operate, the ANN must be trained by a so called Feed-Forward Back-propagation algorithm [49]. This was previously used for an online quantification of high field (HF) and low field (LF) NMR spectra [50], and for the simulation of T_2 -distributions and CPMG-like decay of transverse magnetization from a set of micro-computer tomograph (μCT) images [49].

3. Multivariate analysis

3.1. The general principles of principal components analysis

A complete characterization of the properties of a system involves a series of complex measurements that the values of several parameters are obtained from. Normally these parameters cannot be compared with each other due to their different measurement units. However, when it is necessary to characterize all the measurements, especially if the study assumes the existence of several different groups of samples, this is possible through multivariate analysis. In particular, this is the statistical analysis of the principal components (PCA - principal component analysis), a powerful mathematical tool used in many cutting-edge areas of research.

To understand the simple way of performing the PCA analysis, its principle is described in the followings. Suppose we have a number N of parameters (ranging from $i = 1$ to $i = N$) and a number M of measurements (ranging from $j = 1$ to $j = M$). These correspond to several groups G ($G \leq M$) of samples with characteristic features. The experimental data can be summarized as they are presented in [Table 1](#).

It is customary to calculate the proportion that each principal component contributes to, for the differentiation of the data represented within the principal components, and thus,

$$\text{Proportion}_k = \frac{\lambda_k}{\sum_{k=1}^L \lambda_k} \times 100, \quad (1)$$

where L is the number of principal components, calculated as $L = \min(N, M)$ and where λ are eigenvectors of a covariance matrix (for a detailed mathematical description see [Supplementary Materials section S1: Principal Component Analysis](#)).

One can also calculate the cumulative proportion to observe for example how many principal components are necessary to explain 90 of the diversity of new representations. Therefore,

$$\text{Cumulative Proportion}_l = \sum_{k=1}^l \text{Proportion}_k, \quad (2)$$

so that the total cumulative proportion equals 100%.

Fig. 1. A general review of some low field NMR methods from samples (elastomers such natural rubber or EPDM, polymer exchange membranes, porous materials, biological tissues, and many more), instruments (homogenous magnetic field NMR spectrometers, unilateral inhomogeneous magnetic field NMR sensors like some representatives of NMR-MOUSE, MRI tomograph), raw data (simple FID, popular CPMG, double quantum build-up curve, self and spin diffusion data), primary analysis (Fourier and Laplace-like transform), secondary analysis usually Fourier and Laplace-like spectra deconvolution, pore size assessment, parameter maps, tertiary analysis which can be a multivariate statistical analysis, and a proposed classification or regression analysis using an artificial neural network.

The most interesting result is obtained by calculating the contributions (*loadings*) of the values of the main components, using the relationship,

$$Contribution_{k,i} = \sqrt{\lambda_k} \Lambda_{k,i}, \quad (3)$$

where Λ is the matrix of eigenvalues. That yields a new matrix. The form of this matrix is presented in Table 2. Here $Cont_{par_j}^{PC_k}$ represents the contribution of the Par_j parameter to the main component PC_k . For each graphically represented component (starting with PC_1 , which has the highest proportional contribution), the most signifi-

Table 1

A general matrix that combines the values of measured parameters (Par_1 to Par_N) in groups (Gr_1 to Gr_g) of measurements (M_1 to M_M) for a general statistical analysis in principal components.

		Par_1 [M.U. ₁]	Par_2 [M.U. ₂]	...	Par_i [M.U. ₂]	...	Par_N [M.U. _N]
Gr_1	M_1	$Val_{M_1}^{P_1}$	$Val_{M_1}^{P_2}$	...	$Val_{M_1}^{P_i}$	...	$Val_{M_1}^{P_N}$
	M_2	$Val_{M_2}^{P_1}$	$Val_{M_2}^{P_2}$	...	$Val_{M_2}^{P_i}$	...	$Val_{M_2}^{P_N}$
Gr_k	M_j	$Val_{M_j}^{P_1}$	$Val_{M_j}^{P_2}$	...	$Val_{M_j}^{P_i}$	...	$Val_{M_j}^{P_N}$
	M_{j+1}	$Val_{M_{j+1}}^{P_1}$	$Val_{M_{j+1}}^{P_2}$	...	$Val_{M_{j+1}}^{P_i}$	...	$Val_{M_{j+1}}^{P_N}$
Gr_g	M_{M-1}	$Val_{M_{M-1}}^{P_1}$	$Val_{M_{M-1}}^{P_2}$	...	$Val_{M_{M-1}}^{P_i}$	...	$Val_{M_{M-1}}^{P_N}$
	M_M	$Val_{M_M}^{P_1}$	$Val_{M_M}^{P_2}$	...	$Val_{M_M}^{P_i}$	...	$Val_{M_M}^{P_N}$

Table 2

A general matrix presenting the contribution of all parameters to each of the principal components PC.

	PC_1	PC_2	...	PC_k	...	PC_L
Par_1	$Cont_{par_1}^{PC_1}$	$Cont_{par_1}^{PC_2}$	...	$Cont_{par_1}^{PC_k}$	...	$Cont_{par_1}^{PC_L}$
Par_2	$Cont_{par_2}^{PC_1}$	$Cont_{par_2}^{PC_2}$	...	$Cont_{par_2}^{PC_k}$	...	$Cont_{par_2}^{PC_L}$
...	...	...	...	...	...	...
Par_i	$Cont_{par_i}^{PC_1}$	$Cont_{par_i}^{PC_2}$	...	$Cont_{par_i}^{PC_k}$	...	$Cont_{par_i}^{PC_L}$
...	...	...	...	...	...	...
Par_N	$Cont_{par_N}^{PC_1}$	$Cont_{par_N}^{PC_2}$	...	$Cont_{par_N}^{PC_k}$	...	$Cont_{par_N}^{PC_L}$

cant contributions are thus sought (with the value $Cont_{par_i}^{PC_k}$ the largest, whether positive or negative) and the most significant parameters are thus found.

3.2. Application of PCA analysis in LF-NMR

The regular application of PCA analysis to NMR spectroscopic data requires to consider each chemical shift value as a parameter and to feed the algorithm with a series of Fourier spectra acquired for samples belonging to several groups [46,47]. In LF-NMR this strategy may not always work. Firstly, the magnetic field may not be homogeneous enough to obtain a resolved Fourier spectrum. Therefore, a certain value of the chemical shift may result from the superposition of two or more elementary spectra. These would originate in various functional groups in a sample having a certain degree of complexity. Secondly, this strategy cannot be applied on Laplace-like spectra. In a Fourier spectrum the change in the concentration of a certain component of a complex sample leads to a change in the intensity of the peak located to a well-defined chemical shift (in reality also the position of the peak is subjected to a small variation due to the changes of the studied spin with a modified environment). For a Laplace-like spectrum the variation of dynamics of a certain reservoir of spins leads to a change in the corresponding peak position. Therefore, the PCA analysis may only be applied to a quantification of Fourier or Laplace-like spectra.

For a better understanding of the mechanisms of PCA statistical analysis, one considers a series of data originated from *in vivo* MR-spectroscopy measurements. A number of 52 spectra were recorded using a GE (General Electric) 3 T NMR tomograph. In use, worldwide, in medical Radiology Departments there are mainly two types of NMR tomograph, of 3 T and of 1.5 T (a true LF-NMR). These have similarly performances (even better for newer 1.5 T NMR tomograph compared to our own). Therefore the discussion of our results is not influenced by the exact value of the static magnetic field. The voxel was placed on the uterine

area of 52 women, of which 38 healthy volunteers and 14 ill suspect patients. Of the latter 14, seven patients have been diagnosed with endometrial cancer and seven with uterine cervical cancer. The informed consent was obtained for experimentations from all women, volunteers or patients. For the normal uterus the voxel (ROI – region of interest) dimension (of a rectangular shape) was chosen as large as possible. For the cancerous uterus the voxel size was selected as large as possible, but still within the cancerous area boundaries. The raw data were saved on an external memory drive and a primary analysis (zero filling, Lorentzian apodization, phase correction) was performed using a dedicated jMRUI (Java-based graphical Magnetic Resonance User Interface) version 6.0, a download-free software developed by an international consortium. The raw spectrum was saved as text data in order to be loaded into another dedicated software written in Processing version 3.3.6 (an open source developed at MIT – Massachusetts Institute of Technology), for metabolites quantification. All particular features of these steps were presented in detail in our previous work [16]. From a list of more than 40 metabolites and 10 particular macromolecules, for this example we selected 9 metabolites and water. The parameters for PCA analysis were the concentrations of NAA (N-Acetylaspartic acid), tCho (total Choline), Creatine, Glucose, Lac (Lactate), Macromolecules (sum of all 10 particular macromolecules, MM), Valine, Water, IMCL (intramyocellular lipids) and EMCL (extramyocellular lipids). The input data were introduced in a table format similar to Table 1. For the effective analysis we wrote our own procedure in MatLab R2019a (Academic license provided for Romania by Gamax Laboratory Solutions Ltd., Budapest, Hungary), based on the mathematical equations described in the previous section. The results were validated by another software, PAST (PAleontological STatistics) Version 3.25. The PCA analysis is available also in Origin Professional version and in R software. We preferred our own version, in order to have a better control and to have access to more information than is regularly provided. The graphical representation was performed in Microsoft Excel. The result is complex, but the most meaningful is the main

analysis, i.e. the two dimensional plot of PC1 scores versus PC2 scores (values), the first two columns of matrix D (see Eq. (10) from Supplementary Material).

The main analysis PC1 vs PC2 for our data set (three groups of spectra recorded for 38 healthy uterus specimens, 7 for uterus specimens with endometrial cancer and 7 for cases with uterine cervical cancer) is presented in Fig. 2. With one exception, the points (green triangles) representing the measurements assigned to uterine cervical cancer cases are grouped at negative PC1 values, between -2.26 and -0.88 , and range between -0.98 and 0.32 for PC2 values. For the patient no. 3 the data in PCA main representation was localized at a large PC1 positive value (2.9) and a negative PC2 value (-1.7). The data points for endometrial cancer are more dispersed, having the experimental points assigned to two patients localized at positive PC1 values. More dispersed data correspond to volunteers with normal, healthy uterus. One can also observe a large overlap of data in the range of -3 to 0 for PC1 and from -2 to $+2.1$ for PC2. Normally, this degree of separation is not enough for a robust and unequivocal diagnosis method. In this example, it is possible to move further with the analysis, using the ANN. The details regarding the artificial neural network will be discussed later in Section 4.2.

In the two-dimensional plot shown in Fig. 2, PC1 and PC2 are associated to the loadings (or contributions) of each parameter. In Fig. 3, these loadings are presented for all the 10 components, i.e., the 9 metabolites and water: for PC1 (Fig. 3a) and for PC2 (Fig. 3b). In this interpretation the sign of the loading is not important. Thus, the value of -0.8820 obtained for water makes this parameter the most important in the separation of groups along PC1 (see Fig. 3a). The next important parameter is the concentration of Macromolecules (0.8074), followed by NAA (N-Acetylaspartic acid) with a value of 0.5839 and IMCL (intramyocellular lipids) with a value of 0.5121 . Of a lesser importance in the dispersion along

PC1 is the level of Lactate (0.0944). Contrary, Lactate (0.524) plays an important role in the dispersion of data along the second principal component. Other important parameters are the concentration of total Choline, tCho (0.5844) and NAA (0.6165). The most important role in PC2 dispersion is that of the Glucose level (0.6943). The less important role is played by Macromolecules (-0.0449). In conclusion, the interpretation of a two-dimensional plot of two principal components (PC) should all the time be associated with the analysis of their corresponding loading values.

Another parameter that is important for the degree of separation and the relevance of the results obtained is given by the proportion that each component contributes with, to the total dispersion of data. A test of relevance is given by the number of principal components that must be considered to have a cumulative proportion larger than 90%, or in some cases, larger than 95%. In our example we analyzed a number of 52 measurements (concentrations measured from *in vivo* LF-NMR spectra) and 10 parameters (9 metabolites and water). In this case the number of principal components is 10. It is calculated as the minimum between the number of measurements and the number of parameters (see Section 3.1). The principal components are ordered in decreasing order of their associated proportions (see Fig. 4a). This is also the order of their associated eigenvalues, λ (Fig. 4b). From Fig. 4a, one can see that the proportion that PC1 contributes with to the total dispersion is only $\sim 26.2\%$. Cumulated with the proportion of PC2 ($\sim 15.9\%$), PC1 and PC2 can only explain $\sim 42.1\%$. This means that the data are not well separated. This result is in agreement with the visual observation of the main analysis shown in Fig. 2. Then, from Fig. 4a one can observe that in order to explain more than 90% separation in our data, at least 7 principal components have to be considered.

For a given problem, the PCA analysis is not unique. More parameters can be added and some parameters (with a reduced relevance) can be excluded. For example, in our case one can adjust

Fig. 2. The results of PCA (principal components analysis) for three groups of women (normal/healthy volunteers – group 1; patients with endometrium cancer - group 2; subjects with uterine cervical cancer - group 3) using as input the concentration of 9 metabolites and of water, as they were measured from *in vivo* NMR spectra.

Fig. 3. The loading values corresponding to NAA (N-Acetylaspartic acid), tCho (total Choline), Creatine, Glucose, Lac (Lactate), Macromolecules, Valine, Water, IMCL (intramyocellular lipids), EMCL (extramyocellular lipids) for a) principal component 1 (PC1) and b) principal component 2 (PC2).

the type and number of metabolites. Once the relevant set of metabolites was identified, the analysis can be further extended, as the metabolites are the end products of metabolic processes. On the other hand, in our case different types of parameters can be added, and a parametric map can be associated to the spectroscopic data including the average transverse relaxation times, T_2 , T_1 or ^1H spin density ρ_{1H} . Furthermore, in this particular example, the age, the number of births, the day of the menstrual cycle or eating habits can also add to the relevant set of parameters.

4. Artificial neural network

4.1. General architecture of an artificial neural network

An artificial neural network can be simply defined as a numeric machine learning by examples. Such a machine that is able to be trained to learn can take over complex tasks. Eventually it becomes capable to solve problems for which it is difficult to provide a simple-model solution, can rapidly process large amounts of data,

and it can give an educated prediction in real time [50]. ANNs are worldwide implemented for image recognition, posture recognition, speech recognition, etc. It can also be applied in science. There are recently reported applications for the quantitative and qualitative Fourier spectroscopy [50,51] and for Laplace-like spectroscopy [49].

In Fig. 5 the general architecture of an artificial neural network is presented. It consists of a series of nodes (neurons) and connections between nodes. These nodes are arranged in layers. Each of these layers has a well-defined role. A simplest ANN has at least three layers, but a basic unit can consist of only one single neuron called a perceptron [52]. The input data is received (perceived) by the first layer, called the input layer (blue circles, vertically arranged on the left side in Fig. 5). The last layer is the output layer, from where the data are collected (red circles, vertically arranged, on the right side in Fig. 5). Between the input and the output layers there are a number of hidden layers (green, vertically arranged in Fig. 5). Between each layer and the next one, there is a series of connections. If all the nodes of a layer are connected with all the

Fig. 4. a) Proportions (blue diamond) and cumulative proportion (red square), and b) variance (eigenvalues) - as resulted from PCA analysis of metabolites and water for the three groups of women for all ten principal components. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

nodes of the next layer, then the network is called dense. If not, it is called sparse. By setting some links to a zero weight, the connection is lost, therefore a sparse network is a particular case of a dense one, and therefore from here on, one will consider the full connections. The number of nodes for each layer is independent on the number of nodes of the rest of layers. In Fig. 5 N_i denotes the number of nodes in the input layer. N_{H1} , is the number of nodes of the first hidden layer, and N_{Hn} , the number of nodes of the last hidden layer. N_o is therefore the number of nodes of the output layer. From the mathematical point of view, the data can be stored in a matrix form. The values of input data can be then written as a 1D matrix (a vector),

$$\mathbf{I} = [I_1 \ I_2 \ \dots \ I_i \ \dots \ I_{N_i}] \quad (4)$$

similarly, the output data can also be written as a 1D matrix,

$$\mathbf{O} = [O_1 \ O_2 \ \dots \ O_i \ \dots \ O_{N_o}] \quad (5)$$

The connection between two adjacent layers can be written as a 2D matrix, the weighted matrix, $\mathbf{W}$. For example, the weighted matrix between the input layer and the first hidden layer can be written as,

$$\mathbf{W}^{(I,H1)} = \begin{bmatrix} W_{1,1}^{(I,H1)} & W_{1,2}^{(I,H1)} & \dots & W_{1,j}^{(I,H1)} & \dots & W_{1,N_{H1}}^{(I,H1)} \\ W_{2,1}^{(I,H1)} & W_{2,2}^{(I,H1)} & \dots & W_{2,j}^{(I,H1)} & \dots & W_{2,N_{H1}}^{(I,H1)} \\ \dots & \dots & \ddots & \dots & \ddots & \vdots \\ W_{i,1}^{(I,H1)} & W_{i,2}^{(I,H1)} & \dots & W_{i,j}^{(I,H1)} & \dots & W_{i,N_{H1}}^{(I,H1)} \\ \dots & \dots & \ddots & \dots & \ddots & \vdots \\ W_{N_i,1}^{(I,H1)} & W_{N_i,2}^{(I,H1)} & \dots & W_{N_i,j}^{(I,H1)} & \dots & W_{N_i,N_{H1}}^{(I,H1)} \end{bmatrix} \quad (6)$$

Before being transmitted to the next layer, these values pass to an activation function that can be seen as a gate. The values corresponding to the previous layer are passed across this gate to a current neuron, and if the neuron is activated, this generates output values that will be transmitted to the next layer. From the practical point of view, the activation functions are simple mathematical equations that can determine the output level of a neural network. Such a function is then attached to each neuron. Based on whether the input of each neuron is relevant or not for the model prediction, the activation function determines whether if the specific neuron should be activated (or *fired*, in fMRI terms) or not. The activation functions also play the role of normalization. The output

Fig. 5. The schematic representation of a general architecture of an artificial neural network with an input layer of N_i neurons (number of input data points), a number of Hn hidden layers, each with N_{Hn} neurons, and an output layer with N_o neurons (number of output data points).

value of each neuron is set to a range between -1 and 1 or between 0 and 1 . There are multiple types of activation functions. In the early days of ANN, the sigmoidal activation function was used. At present, binary step functions are also used, as linear or non-linear activation functions. The ReLU (Rectified Linear Unit) activation functions present some advantages and some disadvantages. Some of these disadvantages are Leaky ReLU, or parametric ReLU

tional neuron is added to each layer (with the exception of the output layer). This neuron will not receive data. It is called bias and is drawn on the bottom of each layer in Fig. 5. Then, from the mathematical point of view, the process of feed-forward from input to output layer assumes the successive application of the following matrix multiplication, exemplified for the input and the first hidden layer.

$$f_{act}^{(I,H1)} \left([I_1 \ I_2 \ \dots \ I_i \ \dots \ I_{N_i}] \times \begin{bmatrix} W_{1,1}^{(I,H1)} & W_{1,2}^{(I,H1)} & \dots & W_{1,j}^{(I,H1)} & \dots & W_{1,N_{H1}}^{(I,H1)} \\ W_{2,1}^{(I,H1)} & W_{2,2}^{(I,H1)} & \dots & W_{2,j}^{(I,H1)} & \dots & W_{2,N_{H1}}^{(I,H1)} \\ \dots & \dots & \ddots & \dots & \ddots & \vdots \\ W_{i,1}^{(I,H1)} & W_{i,2}^{(I,H1)} & \dots & W_{i,j}^{(I,H1)} & \dots & W_{i,N_{H1}}^{(I,H1)} \\ \dots & \dots & \ddots & \dots & \ddots & \vdots \\ W_{N_i,1}^{(I,H1)} & W_{N_i,2}^{(I,H1)} & \dots & W_{N_i,j}^{(I,H1)} & \dots & W_{N_i,N_{H1}}^{(I,H1)} \end{bmatrix} + [b_1^{(I,H1)} \ b_2^{(I,H1)} \ \dots \ b_i^{(I,H1)} \ \dots \ b_{N_{H1}}^{(I,H1)}] \right) \quad (7)$$

activation functions. It is beyond the scope of this work to discuss more about the activation functions. A particularity of the activation function is the output domain. This domain may be out of the designated value. In order to correct this problem, an addi-

or into a restrained matrix form,

$$H_1 = f_{act}^{(I,H1)} (I \times W^{(I,H1)} + B^{(I,H1)}) \quad (8)$$

where $\mathbf{I}$ is the 1D matrix of input data, $\mathbf{W}^{(I,H1)}$ is the 2D matrix of weight between input and the first hidden layer, $\mathbf{B}^{(I,H1)}$ is the 1D matrix of bias between input and the first hidden layer, and, finally $\mathbf{H}_1$ is a 1D matrix containing the values of the first layer. The activation function between input and the first hidden layer is $f_{act}^{(I,H1)}$. The information is propagated forward by the so called feedforward procedure by repetitively applying Eq. (8),

$$\mathbf{H}_n = f_{act}^{(H_{n-1}, H_n)} \left(\mathbf{H}_{n-1} \times \mathbf{W}^{(H_{n-1}, H_n)} + \mathbf{B}^{(H_{n-1}, H_n)} \right), \quad (9)$$

and the last step is then,

$$\mathbf{O} = f_{act}^{(H_n, O)} \left(\mathbf{H}_n \times \mathbf{W}^{(H_n, O)} + \mathbf{B}^{(H_n, O)} \right). \quad (10)$$

From Eqs. (7)–(10) one can observe that the activation function can be chosen to be of the same type for all layers or of different types. The output result is compared with the actual result and an error can be calculated for all the elements of the output matrix. The artificial neural network is trained by repetitively calculating the output prediction, compared with the actual result, calculating the errors, and adjusting all weighted and bias matrices. This is performed via a similar process called backpropagation, from the output layer to the input, step by step. For more details on the mathematical aspects, the book of T. Rashid [53] shows how anyone can make their own neural network.

A set of inputs and the corresponding designated output data is called a training data set. Using one such set of training data is called training the ANN for an Epoch. The data from a set can be used systematically or, more efficiently, randomly. Usually the training process implies the repetitive use of the training data set for several Epochs. The performance of the training process can be quantified by calculating the loss, or the mean square root (χ^2),

$$\chi^2 = \frac{\sqrt{\sum_{j=1}^{N_0} \left(O_j^{\text{predicted}} - O_j^{\text{actual}} \right)^2}}{N_0} \quad (11)$$

If a neural network has only one hidden layer between the input and the output layers, then the neural network is called shallow. If the ANN has (commonly) between 2 and 8 additional layers of neurons, then it is called a Deep Neural Network (DNN). There are ANNs with an architecture of simple multilayer perceptron (MLP) [50,52,53]. For MLP all the nodes between adjacent layers are connected. It performs well for 1D uncorrelated input data. For multidimensional input data like a 2D Fourier spectrum or Laplace-like correlation maps, or even for an arbitrary image (in particular MR images), the spatial dependence is important. Therefore, before feeding the artificial neural network, a convolutional layer is implemented to correlate the spatially connected data points. Such an ANN is called convolutional neural network (CNN). It is assumed that such a CNN works well with a 1D spectrum as well. Among the classical problems that can be solved using an ANN is the classification of data or regression [50].

4.2. Application of ANN to cancer classification

In Section 3.2 we discussed the separation of data after a PCA analysis of metabolites concentrations. The initial data were measured *in vivo* by MR-spectroscopy for the uterine area of 38 control volunteer women with healthy uterus, 7 women with endometrial cancer and 7 women with uterine cervical cancer. A visual inspection of Fig. 2 correlated with a low value of cumulative proportion for PC1 and PC2 (~42.1%) show that after a PCA analysis with the chosen parameters, the healthy subjects and the ill cases are not well-separated. This can lead to some problems for a medical diagnosis based only on these results. Nevertheless, this is a standard classification problem for an Artificial Neural Network.

Following the examples of Daniel Shiffman [52], an ANN was implemented into a program written in JavaScript using the machine learning library *ml5* version 0.4.3. The JavaScript environment was chosen due to its feature of easily being shared between users via Internet. The 52 data points with spatial coordinates PC1 and PC2 constituted the input data for our ANN (see Fig. 6a). The association with types of cancer (normal/healthy control group: no cancer (N - class), endometrial cancer (E - class), and uterine cervical cancer (U - class)) represent the output result. The data interpretation program was trained for 10 000 epochs, and then the ANN was ready to predict results. For that, the user must simply set a point (in the PC1, PC2 coordinate system) and the network predicts the most probable type of cancer. In fact, the result available from ANN is the probability percentage for all the classes. This is useful for points localized in areas characterized by large overlapping of data points associated with normal/healthy and cancerous uterus, respectively. If this prediction is performed for all the points in the area of definition for PC1 and PC2, probability maps can be obtained for all the classes. These are presented in Fig. 6b for normal/healthy cases – no cancer, in Fig. 6c for patients with endometrial cancer, and in Fig. 6d for subjects with uterine cervical cancer. In red are presented the areas with a probability greater than 92%. The blue data points present the areas where the probability is less than 8%. One can observe: (i) the large extension of areas for normal/healthy cases (Fig. 6b); (ii) the localization with high probability of cases with endometrial cancer, as a diagonal stripe (Fig. 6c), and (iii) a localized area at the bottom of PC1, PC2 plot, with an extension towards negative PC1 and an increase in the PC2 values for the cases of uterine cervical cancer (see Fig. 6d). In conclusion, the classification resulted from such ANN prediction, especially in the case of overlapping data points in PCA analysis, can be a useful instrument in medical diagnosis giving access not only to a visual inspection but providing the percentages for each type of cancer or normal state of health.

4.3. Application of ANN to an inverse Laplace-like problem

An artificial neural network (ANN) can only accept normalized input data values. Processing the normalized input data results in a set of output data values, representing a normalized percentage associated with each output node (or neuron). This is exactly the definition of the one-dimensional inverse Laplace-like transform applied to relaxometry data recorded in –but not limited to– LF-NMR. In order to illustrate this idea, a CPMG decay was chosen for the input data, and the corresponding T_2 -distribution for the output data. The CPMG mono- or multi-exponential decay can always be normalized to the initial point (or to the maximum, since especially in inhomogeneous fields the first echo is not the highest one [1]). The T_2 -distribution in logarithmic scale is normalized such that the integral area is 1. To solve the inverse Laplace-like problem is not trivial. This is an ill-conditioned problem, in the sense that a small change in the initial data (the measured magnetization) can lead to ample changes in the Laplace-like spectrum [7]. The inverse Laplace-like problem assumed that for an input data set (the magnetization of a spin system) $M(\tau)$, it is required to determine a distribution function (the Laplace-like spectrum) $F(T_2)$, if between these two there is a relationship [7] described by the equation,

$$M(\tau) = \int F(T_2) e^{-\frac{\tau}{T_2}} dT_2, \quad (12)$$

where the transverse relaxation was the parameter of choice. This can be written in a discrete matrix form [7],

Fig. 6. Spatial distributions along PC1 and PC2 of the PCA analysis results, presented in Fig. 2 and the probability to find: (a) normal/healthy cases; (b) endometrial cancer cases, and (c) uterine cervical cancer cases, resulted from a classification analysis using an artificial neural network ANN.

$$\mathbf{M} = \mathbf{K}\mathbf{F} + \mathbf{N}, \quad (13)$$

where $\mathbf{M}$ and $\mathbf{N}$ are the measured magnetization and the noise 1D matrix (vectors) of the same dimension, $\mathbf{F}$ is the desired distribution (a vector with the same or different dimension than $\mathbf{M}$), and $\mathbf{K}$ is the exponential kernel matrix. The matrix form of the inverse Laplace-like problem (Eq. (12)) is similar to one of the Eqs. (8)–(10). The ill-conditioned character of the Laplace-like transform comes from the fact that many solutions may satisfy the criterion [7,38],

$$\|\mathbf{M} - \mathbf{K}\mathbf{F}\| < \epsilon, \quad (14)$$

where $\|\cdot\|$ is the vector norm and ϵ is the noise variance. A possible method to solve the problem consists of the using a Tikhonov regularization term, and to minimize the expression [7,38],

$$\|\mathbf{M} - \mathbf{K}\mathbf{F}\|^2 + \alpha\|\mathbf{F}\|^2, \quad (15)$$

where α is a regularization parameter. Unfortunately, the solution ($\mathbf{F}$) is strongly dependent on the regularization parameter α . In this sense, the width, as well as the number of peaks in Laplace-like spectrum (e.g. the T_2 -distribution) can vary, depending on the α value. There are methods to choose this value for the regularization parameter α . These can be automatic or the user can manually select the value of α . Though, there will always exists a degree of uncertainty related to the trust in the obtained Laplace-like distribution. Based on our previous experience, we find that the algorithm developed for a fast Laplace inversion (FLI) described extensively in [38] is reliable.

In order to test the possibility to use the ANN to solve a problem as those of Laplace-like inversion, a simple artificial neural network with three layers was constructed in JavaScript. Firstly, a series of target data were randomly generated. These were the T_2 -

distributions with fixed width, normalized and with a single component with its maximum are randomly produced within certain limits of T_2 -values. The data length is of 101 points. From these distributions, the corresponding synthetic magnetization decays are calculated for 101 points. The echo-time was chosen to produce a meaningful decay for all the possible T_2 -distributions. A series of 1000 of such pairs are generated and used to train the ANN. This consists of three layers. The hidden layer was chosen to have $2^3 = 8$ times more points than the input data, resulting in 808 points. The ANN was then trained for 10 000 Epoch. The progress

was monitored by calculating the mean square root, χ^2 parameter after each Epoch. The results are presented in Fig. 7 for some testing distributions.

The ANN was able to learn quite rapidly about the shape and width of the T_2 -distribution (see Fig. 7a). Unfortunately, it was not able to learn so fast about the position of the peak. The result presented in Fig. 7b was obtained after a reinitialization of the ANN, because the initialization of weighted matrices $\mathbf{W}$ was performed with random numbers. A convolutional layer may further be needed [50].

The learning performances of our two discussed problems (PCA analysis and Laplace-like inversion) are presented in Fig. 8. Thus, Fig. 8a shows a screen capture with the loss calculated by *ml5* v0.4.3 library during the training for 10 000 Epochs. It can be observed that the loss (uncertainty in prediction) at the end of the Epoch is at $\sim 40\%$ from those calculated at the beginning. Fig. 8b presents an evaluation of the ANN performance in solving the Laplace-like problem. After approximately 100 Epochs, the ANN learns about the distribution shape. Nevertheless, the constructed ANN is not yet optimal to properly learn about the posi-

Fig. 7. Synthetic (simulated) T_2 distributions (blue circles) of 101 points and predicted distribution of 101 points using an artificial neural network with three layers for trained data (a) and (b). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 8. The training parameter: (a) loss values as they were calculated for the PCA data shown in Fig. 2, trained for 10,000 epochs, using an ANN build on top of ml5 version 0.4.3, and (b) and the loss value (χ^2) calculated for a Laplace-like problem trained for 1000 Epochs, using the Shiffman's Artificial Neuronal Network architecture with three layers (101 points for input data, 808 points for hidden layer and 101 points for output data).

tion of peaks. At this stage, it is not the purpose of this work to extend the discussion in this direction, but it will be a subject of interest in our future investigations.

5. Perspectives for low field NMR

• The use of advanced analysis

Low magnetic field is no longer an impediment for advanced NMR characterization of various types of materials. Homogeneous fields are already created, and one and two dimensional Fourier spectroscopy becomes common analytical method. Primary and secondary analyses can be performed for every studied sample. Tertiary and quaternary analyses can be performed for samples grouped in series, having common features, as well as specific differences. The principal component analysis represents a statistical algorithm that allows data of different types to be analyzed in common. It is predictable that such analysis can be extended, for example by increasing the number of measured LF-NMR parameters. After applying PCA, the relevance of each parameter can be evaluated and the most relevant ones will be maintained and further used in the analysis. The samples classification can be performed after a training of different but dedicated artificial neural network with real or synthetic data.

• The use of ANN for a Fourier analysis

An ANN could be used for an analysis of time domain data to get a Fourier spectrum. Though, in this case there is no need to be implemented. The analysis of the Fourier spectra for a classification is another kind of problem, its use has already been reported in many studies [50 and references therein], and one can assume that it will continue to be increasingly applied in such problems.

• The use of ANN for a Laplace-like analysis

ANN was used to predict pore size distribution, transverse relaxation T_2 -distribution and the magnetization decay for porous media. The starting point was a series of micro-CT images [49]. ANN approaches are already versatile in image recognitions. One can assume that the archived performances for Fourier spectra analysis can be transferred to the analysis of Laplace-like distributions of relaxometry or diffusometry LF-NMR data. The main question is if an ANN can solve all the problems related to the solution of the inverse Laplace-like transform of time domain data to a distribution.

As it was discussed in Section 4.3, the inverse Laplace-like transform is an ill conditioned problem. For a strategy to solve a 1D Laplace-like inversion problem using an ANN, a general concept

Fig. 9. The perspective of an Artificial Neural Network capable to solve a 1D ill conditioned problem like those of finding an unambiguous T_2 -distribution from a noisy multi-exponential decay of experimental data.

is proposed. Such a structure may have specialized layers arranged in series or in parallel. In Fig. 9 a possible architecture (in series arrangement) of such an ANN is presented. One can observe that after a convolutional procedure implemented in the input layer, a layer dealing with noise can be implemented (see the [Supplementary Materials Sections S2 The identity test and S3 Noise Reduction](#)). Alternatively, both these procedures can be performed by a single layer. Then one (or more) of such layers can be implemented to recognize the number of components, the position of these and possibly the amplitude of these components (see the [Supplementary Materials Sections S4 Mono-exponential fitting and S5 Bi-exponential fitting](#)). Then another part of this ANN can be trained to recognize the linewidth of these distributions. We were able in this work to show that in this case this is possible. Finally, the linewidth can be convoluted on top of each particular component to obtain the real distribution.

Can it be done? The ANN can be as large as needed, in terms of number of layers and in terms of number of neurons in each layer. The bias can play the role of the regularization parameter, but should be internally defined and not subjected to user manipulation. Parts of these ANN are already demonstrated (see [Section 4.3](#) from this article and sections S2 to S5 from attached [supplementary materials](#)). All of these are not a proof that it can be done, but in case it is possible, it can only be done in this one way.

If done, then how can it be used? The ANN architecture (or model) can be saved and stored. It is enough that one person succeeds, and then the saved model can be accessed via Internet. Then each person can load the model (structure, number and dimension of each layer, the connectivity – weighted matrices, and bias) and can start performing the prediction approaches.

How fast is it? Once the model is loaded, then the prediction is just a problem of some matrices multiplications, addition of biases

vectors, and applying the activation function. One can predict that the solution can be obtained in milliseconds.

Can it be used for high dimensional data? Yes, ANN is already successfully used for image classification. It is just a problem to rewrite the two (or multi) dimensional matrix into a one-dimensional vector. A layer for spatial convolution should also be implemented.

6. Conclusions

We discussed the multiple level analyses of measured data in LF-NMR. The work started with the raw data, then going further up to the quaternary analysis. The emphasis was placed on the tertiary and quaternary analyses. These involve the analysis in principal components (PCA) and the use of an artificial neural network (ANN). Two particular examples were used to highlight the features of each type of analysis. For the principal component analysis, a series of 52 LF-NMR spectra recorded *in vivo* for healthy and cancerous uterus are analyzed. The concentrations of 9 metabolites (NAA – N-Acetylaspartic acid, tCho – total Choline, Creatine, Glucose, Lac – Lactate, Macromolecules, Valine, IMCL – intramyocellular lipids and EMCL – extramyocellular lipids) and of water were the ten parameters of choice. A number of 10 principal components are obtained, while the first 7 of them are required to explain more than 90% of the samples diversity. The main analysis (the plot of PC1 versus PC2) shows a certain grouping tendency for points belonging to uterine cervical cancer. A spatial overlapping of points assigned to healthy and cancerous uterus, respectively, are also observed. The PC1 vs PC2 plot was further explored by using an Artificial Neural Network, implemented in this scope by using JavaScript and ml5 (machine learning) library. The results are presented as 2D maps of probability, which now can be better used for a medical diagnosis. The possible application of an ANN to solve the ill-conditioned problem of Laplace-like inversion is discussed, and a model was suggested to solve sequentially this kind of problems, specific to low field NMR.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jmr.2021.106915>.

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