Improvement in the accuracy of Nuclear Magnetic Resonance spectrum analysis by automatic tuning of phase correction algorithms.

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Abstract.
The aim of the paper was to develop the techniques for automatic tuning of the most popular phase correction algorithms used in NMR spectrum analysis. They were subjected to the parameter optimization and a set of the efficient automatic phase correction algorithms was constructed, resulting in significant increase of the phase error correction accuracy. The mean relative errors calculated for the data driven tuned algorithms were not greater than 5% for both, low and high noise level in contrary to the standard methods that seem to be very noise level dependent.

1. Introduction.

Nuclear magnetic resonance (abr. NMR) is a very popular technique of tumor diagnosis and further treatment. One of its applications is spectroscopy, in which it is possible to detect chemical compounds that are products of cell metabolism. It was proven that different types of tumor cells might be characterized by their specific metabolism. However the metabolite profile of different tumors is very close to each other, thus even a small inaccuracy in the analyzed signal may lead to the wrong judgment [3]. It is then very important to pre-process the signal in such a way that it will contain no unwanted components that may distort the final result. In nuclear magnetic resonance spectroscopy such components are: phase error, noise and baseline. The most important part, from the analytical point of view, is the phase error. The exemplary peak with and without phase error is presented on figure 1.

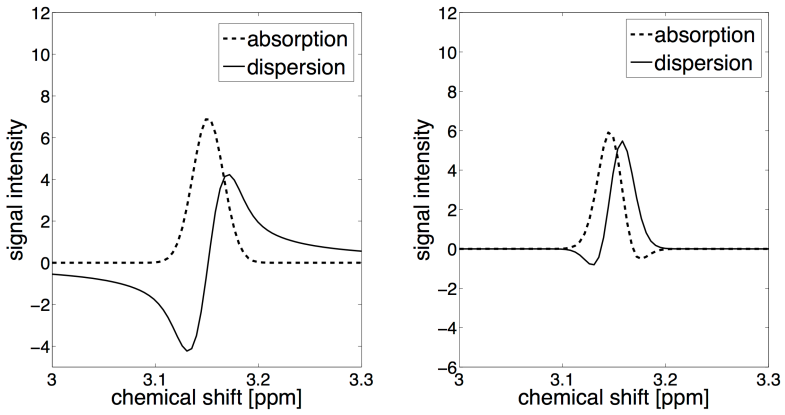

Fig. 1. NMR peak without (left panel) and with (right panel) phase error. Both absorption and dispersion spectra are presented.

In order to eliminate the signal phase error, its model must be identified. It was assumed that phase error might be described by a linear dependence (equation 1). Such a representation is proven to be a good estimate of phase shift for clinical 1H NMR spectra [4]. The linear phase error model contains two parameters: so called zero order components φ_0 and first order component that is frequency dependent:

$$\Delta\varphi = \varphi_0 + \frac{\mathrm{k}}{\mathrm{N}}\varphi_1 \tag{1}$$

where k denotes the index of the spectrum point.

The simplest correction technique is a manual tuning that requires a specialist knowledge and a subjective judgment of human expert [3]. Such a methodology is time consuming and requires a presence of human expert who is not always available. The solution is to design an automatic algorithm that will use a numerical method for phase error model estimation combined with the optimization techniques to minimize the predefined quality criterion being a translation of human expert knowledge to a computer algorithm [1]. There exists number of automatic phase correction techniques. Some of them require the analysis of series of spectra [5], since they assume that phase error may be identified as an additional component in a group of data obtained on a same tissue. In clinical application a series of spectra is not always available and in consequence the methods cannot be widely used. The second group of methods rely on a single spectrum only. Among them, the most popular are: Automics [2], Shannon's entropy minimization [3], Ernst's integral minimization [4], Dispa [5] and eDispa [6]. They give satisfactory results but an improvement of their accuracy may be achieved. The aim of the paper is to develop the techniques for an automatic tuning of the most popular phase correction algorithms used in NMR spectrum analysis.

2. Materials and methods.

Five the most popular phase correction algorithms were chosen and examined.

2.1 Automics.

The algorithm was proposed by Wang et al. in 2009 as a part of their system Automics [6], and is based on the definition of two constant value intervals across the signal – first interval located at the beginning of the spectra, the second at the end. The length of the intervals is not defined by the authors, and no suggestion on their construction is provided. The interval length may be treated as an additional parameter that after proper tuning may improve accuracy of the method. Our automatic tuning algorithm requires only 2 intervals in opposition to 4 proposed originally by the authors. Tuning procedure starts with the minimal length of the intervals (assumed as equal to 2 data points) and the linear regression models with statistical tests on trend inside the interval are applied to each interval independently. If the slopes do not significantly differ from zero value, the additional points increase the interval and the next iteration of calculations is required. If at least one slope is significantly different from zero, which means that a trend is observed among data points, the interval length tuning is completed and it is possible to calculate the parameters of phase error model. The $\Delta\varphi_j$ per every interval can be obtained with the use of modified Automics method formula:

$$\Delta\varphi_j = \operatorname{atan}\left(\frac{R_{j,2}-R_{j,1}}{I_{j,2}-I_{j,1}}\right) = \varphi_{0+}\left(\frac{\frac{k_{j,1}+k_{j,2}}{2}}{N}\right)\cdot\varphi_1 \qquad (2)$$

where index j stands for the location of the interval: $j=1$ for the interval located at the beginning of the spectrum; while $j=2$ for the interval located at the end of the spectrum. $R_{j,2}$ and $I_{j,2}$ are the real and imaginary part of an element at the end of the interval; and $R_{j,1}$ and $I_{j,1}$ are the real and imaginary part of an element at the beginning of the interval, $k_{j,1}$ and $k_{j,2}$ are the indices of the beginning and the end of the jth interval, and N is a length of the spectrum. Having two equations, one per every interval, allows for the estimation of φ_0 and φ_1.

2.2 Optimization based methods.

The next methods were optimized with the use of a novel approach for initial condition estimation as well as the appropriate optimization technique.

2.2.1 Shannon's entropy minimization.

First method in this group is the Shannon's entropy minimization method [7]. It is based on calculation of Shannon entropy of the given NMR absorption spectrum. The minimization problem is given by:

$$\min_{\varphi_0,\varphi_1} H = \min_{\varphi_0,\varphi_1} \left(-\sum_{k=1}^{N} \mathrm{Re}\big(S(k,\varphi_0,\varphi_1)\big) \cdot \ln\left(\mathrm{Re}\big(S(k,\varphi_0,\varphi_1)\big)\right) + P\right) = \min_{\varphi_0,\varphi_1}\left(-\sum_{k=1}^{N} S_A(k,\varphi_0,\varphi_1) \cdot \ln\big(S_A(k,\varphi_0,\varphi_1)\big) + P\right) \quad (3)$$

where H is the Shannon entropy of given spectrum, *Re* denotes the real part of the spectrum, S_A is a magnitude of the absorption spectrum at *kth* data point and P is a penalty factor.

2.2.2 Ernst's integral minimization.

The method was proposed by Ernst [8] and it is based on the minimization of the integral of dispersion spectrum. In ideal case, such an integral should turn to 0. However in real life experiment, due to the existence of the noise, it rarely approaches desired value. In this case problem of optimization is given by:

$$\min_{\varphi_0,\varphi_1} I = \min_{\varphi_0,\varphi_1} \int_a^b \mathrm{Im}(S(x,\varphi_0,\varphi_1))dx = \min_{\varphi_0,\varphi_1} \int_a^b S_D(x,\varphi_0,\varphi_1)dx \quad (4)$$

where *I* is an integral value, *Im* denotes the imaginary part of the spectrum, S_D is a magnitude of the dispersion spectrum; a and b are the integration limits equivalent to the minimum and maximum values on the frequency [Hz] or [ppm] scale of the spectrum.

2.2.3 eDispa.

The next analyzed algorithm is called eDispa [9] and it is based on a predefined Q-factor with the parameters φ_0, φ_1:

$$Q(\varphi_0,\varphi_1) = \sum_{k=1}^{N} \left(\mathrm{Re}\big(S(k,\varphi_0,\varphi_1)\big)\right)^2 \exp\left(\frac{-2\cdot(2k-N)}{N}\right) = \sum_{k=1}^{N}\left(S_A(k,\varphi_0,\varphi_1)\right)^2 \exp\left(\tfrac{-2\cdot(2k-N)}{N}\right) \quad (5)$$

where *Re* denotes the real part of the spectrum, S_A – the magnitude of the absorption spectrum, *k* is the index of data point, *N* is a length of the spectrum and φ_0, φ_1 are parameters of the linear phase error model (Eq.1). The optimization problem is a maximization of the $\eta(\varphi_0, \varphi_1)$:

$$\max_{\varphi_0,\varphi_1} \eta(\varphi_0, \varphi_1) = \max_{\varphi_0,\varphi_1} 2\pi \left(\frac{Q(\varphi_0,\varphi_1) - \min Q(\varphi_0,\varphi_1)}{\max Q(\varphi_0,\varphi_1) - \min Q(\varphi_0,\varphi_1)}\right)^4 \quad (6)$$

2.2.4 Setting up the initial conditions.

The three above mentioned methods are formulated as the optimization problems. An input to every algorithm is a spectrum (absorption or dispersion - depending on the method) corrected by a phase error model (equation 1). Due to the nonlinear character of the optimization problem, the initial values of parameters, named the initial conditions, are crucial for the whole optimization process. The proposed initial condition setting algorithm is based on the properties of a water signal peak, which is located in the middle of the signal range. Assuming that the water peak should have the phase angle equal to 0, one can calculate the rough estimate of the phase error as equal to:

$$\Delta\varphi = \varphi(S_{k_{max}}) \quad (7)$$

where $\Delta\varphi$ is an initial estimate of the phase error, and S stands for the NMR spectrum, index *k* denotes the spectrum data point with maximum spectrum absolute value, so:

$$\max_k(|S(k)|) = |S(k_{max})| \quad (8)$$

The linear phase error model has two parameters, having $\Delta\varphi$ only does not allow for the unambiguous estimates of these. Some extra assumptions are required, thus basing on the numerical simulations and the properties of the 1H NMR spectra we propose to assume the φ_1 vs. φ_0 ratio as equal to 4.

2.2.5 Choosing the optimization algorithms.

After a series of experiments we decided to implement the well-known Nelder-Mead downhill simplex method (abr. NM) [11] to optimize (Eq.3) and (Eq.6). For Ernst optimization problem (Eq.4) the integral global minimization algorithm was applied [12].

2.3 Dispa.

The last phase correction algorithm that was examined in this study was Dispa [10] where the estimation of the spectrum phase error is based on the calculations done for two a priori chosen data points. Since 1H NMR spectra aquisition is not noise free, the obtained estimates of the linear phase error model parameters are very inaccurate. We propose to use a linear regression technique on the phase error estimates calculated for all peaks.

2.4 Validation of algorithms.

In order to determine the reliability of the tuned algorithms the analyses were performed on numerically generated data sets, where all the spectrum parameters, like number of peaks, their location and height are know. The process of the phase error and random noise generation is well defined too. The model for the numerically generated data follows the spectra obtained on "human brain" phantom, and consists of the Lorentzian shape peaks located at the following positions: 0.5 ppm (Lactates), 2.0 ppm (NAA), 3.0 ppm (Creatine), 3.2 ppm (Choline), and 4.6 ppm (Inositol). Some extra peaks were added together with the noise signal uniformly distributed across the spectrum frequency range to reproduce the presence of amino acids, glucose and other metabolites in human brain spectrum. The numerically generated signals with known chemical compound amounts allow for the exact error estimates. The spectra were generated for 4 values of the phase error: 10, 15, 20 and 25 degrees. The numerical experiment was repeated 50 times per every phase error model and additionally for two different noise levels: low and high – SNR equal to 30.75 and 8.52 respectively (400 simulations in total). Scheme of the numerical simulations is presented on Fig. 2.

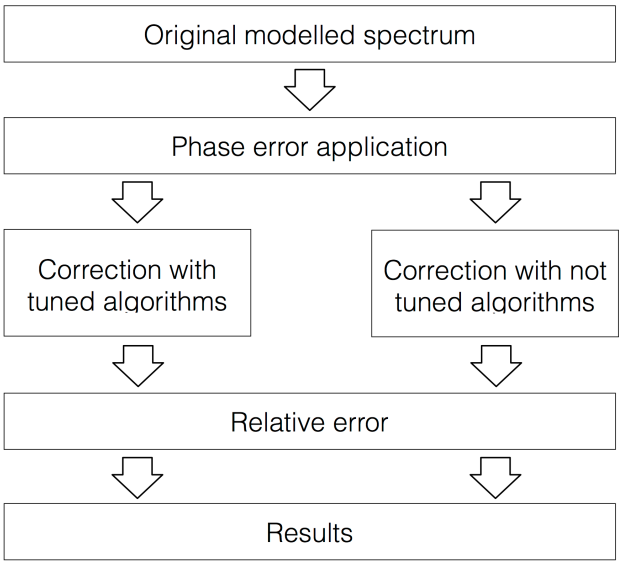

Fig. 2. Scheme of proposed validation experiment. Both tuned and not tuned methods are examined.

3. Results

During the validation of the tuned algorithms a set of NMR spectra's were numerically generated. The exemplary spectrum is shown on Figure 3.

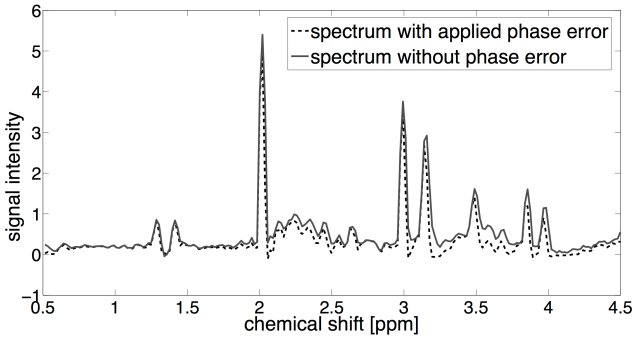

Fig. 3. Exemplary spectrum obtained with the addition of the phase error equal to 10 degrees and low level noise. The original model spectrum (without phase error and additive noise) is also shown.

The performance of the tuned algorithms was examined with the use of so-called "dispa" plot. It is a phase plot obtained for a spectrum, where each peak is represented as an ellipse. The longer diameter of such an ellipse should lie on the OX axis and when it does not, the angle between the axis and the diameter is basically the phase shift. Because in analyzed spectra peaks were tight, the amount of data points per peak is limited. To increase the accuracy of "dispa" plot the ellipses were modelled based on data points. The idea is presented on a Figure 4.

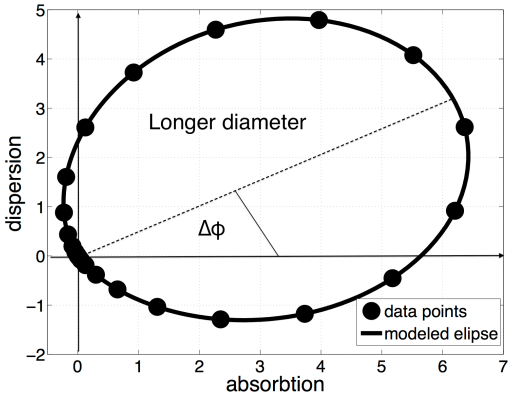

Fig. 4. Exemplary spectrum obtained with the addition of the phase error equal to 10 degrees and low level noise.

All 400 spectra were corrected with the use of tuned and original methods. The correction error [deg], defined as the difference between the estimated and applied phase error, was calculated for every spectrum accompanied by its relative value [%]. The results obtained for low noise are shown on Figure 5 and 7 and in Table 1, while Figure 6, Figure 7, and Table 2 present results for high noise level. For every modelled

phase error value, the mean value from 50 repetitions was calculated as well as their standard deviation (SD).

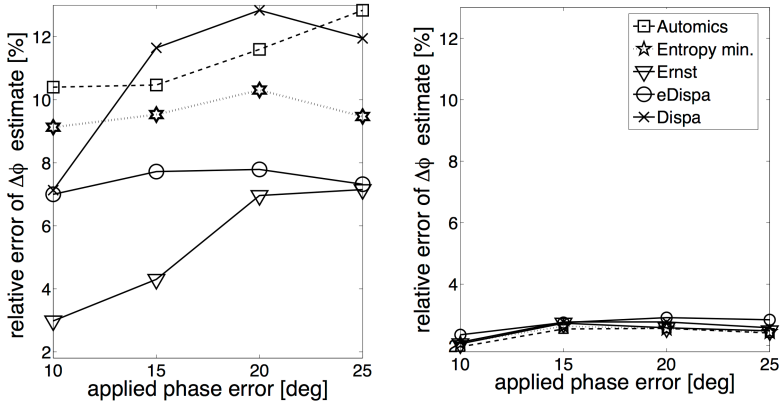

Fig. 5. Graphical presentation of the mean values of the error obtained for the original algorithms for different applied phase error levels (left panel) and the final values obtained with the use of adaptive tuning techniques (right panel). Experiment performed with the low level of noise.

Table 1. Mean of the relative errors of the phase error estimates depending on the method and parameter tuning technique. Experiment performed with the low level of noise.

Applied phase error [deg]	Correction method									
	Automics		Shannon's		Ernst's		eDispa		Dispa	
	Estimated phase error [%]		Estimated phase error [%]		Estimated phase error [%]		Estimated phase error [%]		Estimated phase error [%]	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
No tuning – the original algorithms										
10	10.40	1.14	9.13	0.96	2.98	0.88	7.00	0.96	7.13	1.05
15	10.47	0.99	9.53	0.83	4.30	0.93	7.72	0.84	11.65	1.21
20	11.60	1.21	10.31	1.01	6.96	0.89	7.79	1.10	12.84	1.14
25	12.84	1.18	9.47	0.89	7.15	0.50	7.32	0.98	11.95	1.18
Adaptive tuning of the algorithms										
10	1.96	0.78	2.06	0.57	2.08	0.78	2.35	1.35	2.11	0.92
15	2.54	0.57	2.73	0.50	2.63	0.50	2.75	0.78	2.76	0.71
20	2.56	0.50	2.80	0.43	2.55	0.50	2.91	1.28	2.77	1.07
25	2.41	0.36	2.48	0.36	2.44	0.36	2.84	0.99	2.58	1.08

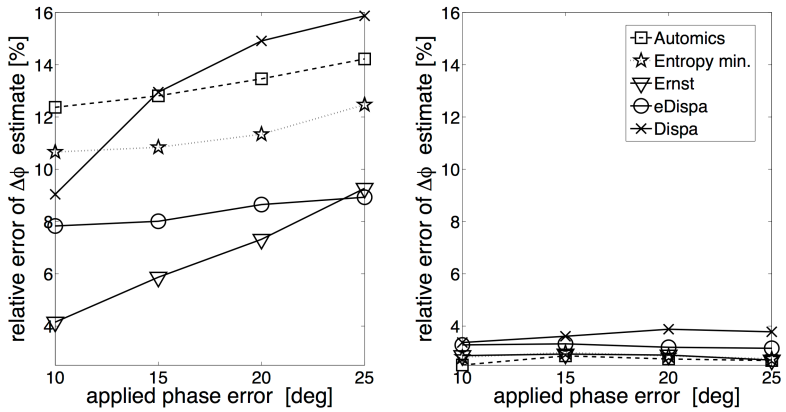

Fig. 6. Graphical presentation of the mean values of the relative error obtained for the original algorithms for different applied phase error levels (left panel) and the final values obtained with the use of adaptive tuning techniques (right panel). Experiment performed with high level of noise.

Table 2. Mean of the relative errors of the phase error estimates depending on the method and parameter tuning technique. Experiment performed with the high level of noise.

Applied phase error [deg]	Correction method									
	Automics		Shannon's		Ernst's		eDispa		Dispa	
	Estimated phase error [%]		Estimated phase error [%]		Estimated phase error [%]		Estimated phase error [%]		Estimated phase error [%]	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
No tuning – the original algorithms										
10	12.37	1.71	10.66	1.96	4.15	1.91	7.83	2.21	9.04	1.95
15	12.81	1.56	10.84	1.63	5.87	2.02	8.01	2.19	12.95	2.05
20	13.46	1.78	11.34	1.45	7.32	1.89	8.65	2.10	14.91	3.01
25	14.22	1.71	12.47	1.58	9.27	1.99	8.93	2.38	15.87	2.71
Adaptive tuning of the algorithms										
10	2.75	0.76	2.92	1.08	2.97	0.95	3.15	1.03	3.07	1.27
15	2.72	0.59	2.87	0.96	3.02	0.98	3.23	1.25	3.55	1.24
20	2.88	0.81	2.97	1.00	2.91	1.06	3.20	1.12	3.73	1.30
25	2.91	0.73	3.01	1.07	2.99	0.98	3.25	1.19	3.69	1.35

As it was expected, the highest impact on Automics method's final result has the size of the intervals that are used for the phase error estimation. An adaptive data driven setting of their length, instead of a strict a priori definition improves the results significantly and makes the methods signal independent. For the next three methods, i.e. Shannon entropy minimization, Ernst integral minimization, and eDispa algorithm, the efficient method of tuning based on simplex method and the optimized initial

parameter estimation combined with the proper initial condition definition was proposed. The increase in correction accuracy is significant. The phase error estimates, obtained in Dispa algorithm, were corrected by incorporating into the error model the knowledge on the phase difference among all peaks. Also in this case, the accuracy increase is noticed. The noise level influences the ability of phase correction for all techniques. By average, the relative error value for all tuned algorithms is not grater than 5% for both low and high noise level in contrary to the original methods. The proposed adaptive tuning of the algorithms seems to be, to some limit, not dependent on noise level.

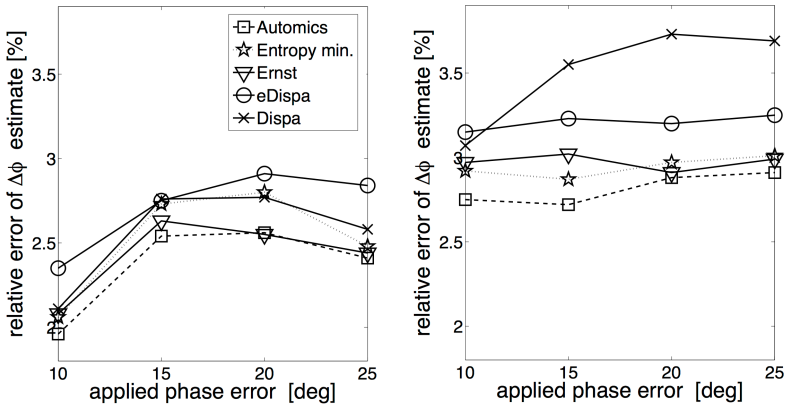

Fig. 7. Graphical presentation of the mean values of the relative error obtained for tuned algorithms. Left panel- simulation for low value of noise, right panel for high level of noise.

4. Conclusions.

As a result of this study, a set of the efficient automatic phase correction algorithms was obtained. All considered methods after the adaptive tuning of their parameters give the satisfactory error phase estimates in numerically simulated experiment. As it could be noticed, the relative error of the signal mean phase error estimates for each examined algorithm is lower than 5%. The highest increase of accuracy was observed for the Automics method. We conclude that adaptive tuning of the algorithm parameters and its numerical implementation play a significant role in the improvement of NMR spectroscopy analysis. All tuned algorithms are a part of the GNMR system which is available on request.

5. Acknowledgments

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6. References

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